The New England
Journal of Medicine

Copyright. 1938, by the Massachusetts Medical Society

VOLUME 218 FEBRUARY 17, 1938 NUMBER 7

THE LOSS OF BLOOD IN CERTAIN STANDARD OPERATIONS FOR MALIGNANT DISEASE

WESTON T. BUDDINGTON, M.D.,* AND GRANTLEY W. TAYLOR, M.D.†

WRENTHAM AND BOSTON

THE determination of the amount of blood lost in operations is of great interest and value. The amount becomes of major importance in a poor-risk patient with malignant disease. A knowledge of the amount lost in certain types of operative procedures not only helps the surgeon to plan the preoperative and postoperative treatment, but also guides him in the choice of a technic.

Relatively little material dealing with this subject has been published. Gatch and Little[1] investigated the amount of blood lost in several of the commoner operations, and presented their results and method in 1924. Coller and Maddock,[2] using the same method, made additional studies to determine what part the loss of blood played in the dehydration attendant upon operations. Recently Pilcher and Sheard[3] have reported a varied series from the Mayo Clinic.

The method which we have employed to determine loss of blood is based on that of Gatch and Little,[1] although modified according to the recommendations of Stewart.[4] Just before operation, from 4 to 6 cc. of blood is withdrawn from a vein and mixed with a few milligrams of heparin. This prevents clotting, without appreciably diluting the blood. Exactly 1 cc. is mixed with known amounts of N/10 hydrochloric acid, to form acid hematin. This constitutes the "standard," generally in a 1:500 dilution.

With rare exceptions, the skin is prepared with 3.5 per cent tincture of iodine. After drying, this is removed with alcohol, to prevent its being absorbed by the sponges and drapes used during the operation, and thus disturbing the calculation of loss of blood. The sponges upon being discarded are dropped into pails of distilled water so that the blood will not dry and cake. All drapes, gowns and instruments stained with blood are washed in distilled water until the hemoglobin has been extracted. The sponges and linen are wrung dry by being passed through a wringer. Tissues removed from the body are washed free of gross blood. The total volume of the solution of laked blood thus obtained is accurately measured, and a measured sample is converted into acid hematin by the addition of hydrochloric acid. This is compared with the standard in a colorimeter. The amount of blood lost is easily calculated from these data.

As judged by our own control tests and those of others, the method is accurate, possibly within 5 per cent or at most 10 per cent of the actual loss. It is impossible to recover all the blood spilled during a major surgical procedure, except perhaps in transurethral resections of the prostate where all the bloody irrigating fluid can be saved.

Our object was twofold: to ascertain the amount of blood lost in some of our standard operations, and to discover the factors affecting this amount. Incidentally, our studies have emphasized in the surgeon's mind the necessity of hemostasis, and have confirmed the advantage of a given technic and the advisability, at times, of postoperative transfusion. The minimum, maximum and average loss of blood for a variety of operations are shown in Figures 1 and 2.

The wide difference in the 2 cases of vaginal hysterectomy accompanied by perineorrhaphy merits comment. In the case where the loss of blood was slight, the patient had a small uterus, which was easily delivered, and the operation was carried out with close attention to hemostasis. The high loss of 935 cc. occurred in a slightly obese patient who had previously had 4800 r units of radiation applied over the operative area, the resulting fibrosis rendering the operation technically difficult. Pilcher and Sheard[3] have reported 1 case of vaginal hysterectomy, with no mention of perineorrhaphy, in which the loss of blood amounted to about 680 cc.

The maximum and minimum figures for abdominal hysterectomy are interesting; both opera-

From the Pondville Hospital, Massachusetts Department of Public Health, Wrentham.

*Chief surgical resident, Pondville Hospital.

†Assistaat visiting surgeon, Pondville Hospital.

tions were performed by the same surgeon. The average of all the cases is close to that of similar ones recorded elsewhere. In almost every case in our series the operation included removal of both tubes and ovaries and the appendix.

There was virtually no difference between the amount of blood lost in a total gastric resection

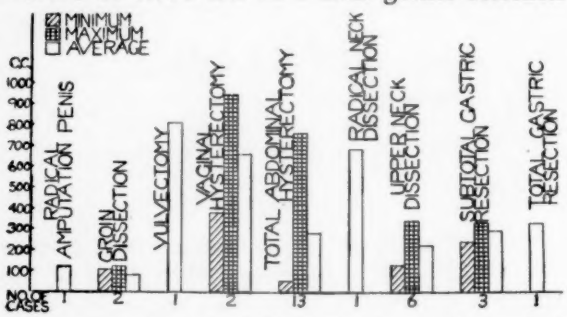


Figure 1. *Amount of blood loss in certain standard operations.*

and that lost in subtotal resections; 2 cases of partial resection are recorded in the literature, one with a loss of 274 cc. and the other with a loss of 232 cc. From all these we may conclude that the desirability of postoperative transfusion in the average gastric resection rests on other grounds than the amount of blood lost at operation.

The results in resection of the rectum are significant. In this procedure we separated the blood

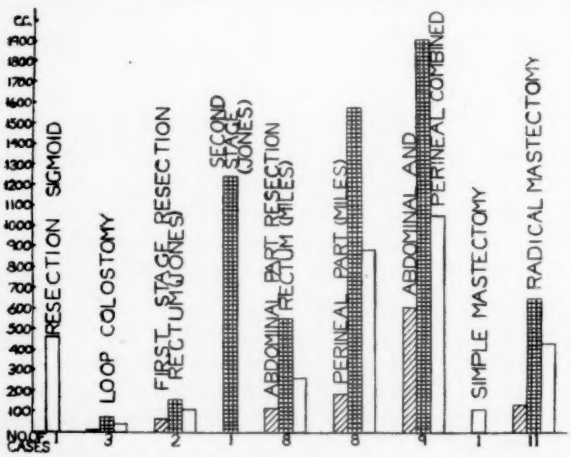


Figure 2. *Amount of blood loss in certain standard operations.*

lost in the abdominal excision from that lost in the perineal. The latter was carried out with the patient either in a lateral position or in that employed for lithotomy. It was at once apparent that most of the loss arose from the perineal excision, even when due allowance was made for blood which had collected in the pelvis in the interval between the two parts of the operation and was thus included in the loss at the time of the second operation. The shock which occasionally developed during the latter part can be attributed in great degree to this sudden loss of a large amount of blood. The total loss is striking, and strongly supports our policy of giving at least one transfusion, and not infrequently two, in such combined procedures. Our routine practice is to have a continuous intravenous saline clysis started at the beginning of the operation; the citrated blood for transfusion being added when the posterior excision is begun.

The average loss for 11 cases of radical mastectomy, all performed according to the same technic, was 430 cc. We were surprised to find in the literature figures for this operation ranging from 725 to 1272 cc. Our lowest loss (134 cc.) occurred in a radical mastectomy performed on a thin, elderly woman with a small atrophic breast. The average systolic blood pressure during the operation was equivalent to only 70 mm. of mercury. Careful attention was given to hemostasis throughout the operation, which lasted one hour and fifty minutes.

The technic employed for radical mastectomy is described elsewhere.[5] It consists essentially in a modification of the transverse axillary dissection of Rodman.[6] The important steps which keep the loss of blood at a minimum are: first, sharp dissection with constant traction, which allows the vessels to be clamped before cutting, particularly the many tributaries of the axillary vein and artery; secondly, deferred removal of the sternocostal portion of the pectoralis major muscle and fascia until the remainder of the dissection has been completed. The latter permits the operator to expose the perforating branches of the internal mammary vessels so that they may be clamped before cutting. The amount of blood that spurts from one of these larger vessels in a very short time is considerable.

During the study, record was kept of several factors which it was felt affected the amount of blood lost; for example, the patient's blood pressure and physique, and the speed and skill of the operator. Correlation of these factors resulted in certain general deductions. A high blood pressure during the operation of course increased the rate of blood flow from the ends of severed vessels. Obesity contributed to a higher blood loss in two ways: first, the additional amount of tissue to be dissected necessitated cutting a great many additional vessels; secondly, accurate and secure application of hemostatic clamps was more difficult owing to the friability of vessels in adipose tissue. When all the factors tending to decrease blood loss operate together, the amount may be unusually small, for example, the 134 cc. for a radical mastectomy referred to above. The technic and skill of the surgeon and his assistants constitute the most significant factor; often, however, a combination

of adverse circumstances — technical difficulties, obesity, hypertension and the like — more than offset the advantages of an efficient operating team. While the amount of blood lost has a distinct bearing on the development of postoperative shock, other influences are also powerful. The character of the anesthesia, the manipulations, the time consumed by the operation, cooling, the rapidity of blood loss and the general condition of the patient all have an important bearing. It is not surprising, therefore, that we were able to establish only a gross correlation between the amount of loss and the clinical evidence of shock. Many of the other factors, however, are similarly under the control of the operating surgeon; and it is probable that the amount of blood lost serves as a measure of the care and skill with which he has carried out his operation, and of the effectiveness of the precautions he has exercised against the development of operative shock.

SUMMARY

1. The loss of blood attendant upon certain standard operations for malignant disease was determined, and the results are recorded.
2. Factors tending to increase or decrease blood loss are briefly discussed.
3. Knowledge of the amount of blood lost in certain types of operations aids the surgeon in planning his operative, preoperative and postoperative treatment.

REFERENCES

1. Gatch, W. D., and Little, W. D.: Amount of blood lost during some of the more common operations. J. A. M. A. 83:1075-1076, 1924.
2. Coller, F. A., and Maddock, W. G.: Dehydration attendant on surgical operations. *Ibid.* 99:875-880, 1932.
3. Pilcher, F., Jr., and Sheard, C.: Measurements on the loss of blood during transurethral prostatic resection and other surgical procedures, determined by spectrophotometric and photelometric methods. Proc. Staff Meet., Mayo Clin. 12:209-213, 1937.
4. Stewart, J. D.: personal communication.
5. Taylor, G. W., and Daland, E. M.: The Greenough technique of radical mastectomy. Surg., Gynec. & Obst. 55:807-811, 1937.
6. Rodman, W. L.: *Diseases of the Breast.* 385 pp. Philadelphia: P. Blakiston's Son & Co., 1908.

THE USE OF SULFANILAMIDE IN GONORRHEA IN THE MALE

A Preliminary Report and a Warning

WALTER M. BRUNET, M.D.,* CHARLES H. REINHARDT, M.D.,† AND NORMAN D. SHAW, M.D.‡

CHICAGO

THIS preliminary report relates to the use of sulfanilamide as an adjuvant in the treatment of several hundred acute and chronic, anterior and complicated, cases of gonorrhea in the male. We have not depended solely upon sulfanilamide for a cure. In acute anterior infections local injections of a mild antiseptic have been given, and in the posterior cases remedies of proved worth have been administered in conjunction with the compound. A number of these patients have been carefully observed for a sufficient period of time for recognized tests of cure to be carried out before they were discharged, and for an evaluation of the treatment. The patients have not been selected, and the clinical study is still in progress and will be reported in detail at a later date.

Within the past twenty years about a dozen "specifics" for gonorrhea have been proclaimed. The most recent one, sulfanilamide, follows close upon the Corbus-Ferry filtrate, which failed miserably as a cure. Despite reports of remarkable cures from the use of sulfanilamide in gonococcal infections in the male, we believe that this infection will continue for many years to be the medical riddle of the sphinx. We believe that sulfanilamide is, and should be, regarded only as an experimental and speculative remedy until a larger number of adequately controlled and correlated clinical studies have been reported. The recent papers giving the results of the use of the drug in specific urethritis have been wholly lacking in completeness, and not a single contributor has mentioned adequate controls or extended supervision. Therefore, on the rather meager grounds of insufficient clinical trial and observation the medical profession is deluged with propaganda announcing another cure for gonorrhea. In a recent leaflet one of the large drug houses describes the action of the drug as follows: "In gonorrhea the discharge disappears within a few days, and smears usually become negative within a week." This is quite simple, and with such a medicament there is surely no occasion for the guiding hand of a physician. Several recent reports in the literature have been to the effect that the toxicity of the drug in man and animals is low. We have seen a large number of patients who showed some reaction to it, but whether these manifestations are toxic in origin or are due to an idiosyncrasy is not known.

Within the past few months there have appeared reports of the use of Elixir of Sulfanilamide which has caused scores of deaths; the fatalities were apparently due to the diethylene glycol in which the drug was dissolved. Sulfanilamide is one of

From the Public Health Institute, 159 North Dearborn Street, Chicago.
*Chief, Urological Department, Public Health Institute.
†Staff member, Urological Department, Public Health Institute.
‡Staff member, Urological Department, Public Health Institute.

a large number of chemical compounds which contain the benzene ring, and it is well known that these products and the closely allied phenyl derivatives often exhibit a harmful effect upon the bone marrow and other blood-making organs. Several authors report the successful use of the medicament in meningitis, bacteremia of puerperal origin, pneumonia and influenza. However, dangerous and even fatal blood changes such as acute hemolytic anemia, agranulocytosis and sulfhemoglobinemia have followed its administration. While these alterations are not often encountered, they occur with sufficient frequency to demand the most careful observation and control of the patient. The indiscriminate prescribing of sulfanilamide by physicians is to be frowned upon, and its direct sale over the drugstore counter is to be severely condemned.

Sulfanilamide in our hands has not yet proved to be a specific for gonorrhea in any stage of the disease, but we do find that its conservative use has been of benefit in a number of cases. We recommend that not more than 40 gr. be taken daily. We prescribe two 5-gr. tablets and an equal amount of bicarbonate of soda, to be taken every three hours. Even this small amount causes unexpected symptoms in a number of patients. We suggest that larger doses be withheld until the pharmacology of the drug has been more thoroughly studied and its action understood, for it is possible that its injudicious use may induce mortality in a disease which ordinarily should have none.

In acute anterior gonorrhea we have observed a number of patients in whom the drug produced fairly prompt changes in the character and consistence of the discharge, but organisms were readily demonstrated for many days in the stained slides. We expect about 5 per cent of our patients with an anterior infection to recover from their disease promptly with mild conservative treatment. By the addition of sulfanilamide to our armamentarium this percentage will probably be doubled. However a number of our patients who have taken large doses of sulfanilamide for many days have developed severe complications, such as prostatitis, vesiculitis and epididymitis, and have had a stormy recovery. We have treated others in whom an apparent carrier state was produced; in these the symptoms almost completely disappeared, but there remained a residual watery but persistent urethral discharge in which typical intracellular gonococci were found. These patients afterward respond slowly to any method of therapy.

Sulfanilamide appears to be of value in lessening the pain and discomfort in acute posterior extensions, and in some cases there is an apparent shortening of the course of the disease. We have seen several patients with chronic, deep-seated infections which had become stationary under other forms of therapy who began to improve within a day or two after taking the drug. The urethral discharge decreases rapidly, the second-glass specimen of urine clears, the pus content of the prostatic secretion diminishes, and a complete recovery follows. The most striking results we have encountered were in 2 patients with acute gonococcal arthritis. In one young man the symptoms were relieved in twelve hours, the redness and swelling of the wrist and fingers being reduced and the pain entirely relieved, and he made an uneventful recovery. In the second patient there was not quite the same dramatic response as in the first, but a complete recovery was made within a few weeks.

The drug probably acts by causing some change in the organism, which permits phagocytosis, and at the same time the growth of the bacteria is inhibited. In many well-developed anteroposterior infections the drug apparently has no effect on the course of the disease.

We have had a large number of patients with mild reactions. These have consisted of anorexia, gastric distress, headache, dizziness, ringing in the ears, dermatitis and elevation of temperature. One patient stated that he became "unconscious" after taking the drug for twenty-four hours. In 2 cases elevated, reddish-brown skin lesions were observed. In several patients with a dermatitis the eruption was present on the palms of the hands but the mucous membrane of the mouth was not involved.

Sulfanilamide may become a very valuable remedy in urological practice, but overenthusiastic manufacturers must not continue to impose upon the credulity of the general practitioner; on the other hand, skeptical physicians should not minimize the value of the drug without sufficient trial. The place the compound will occupy in medical practice must depend upon time and the unbiased sifting of divergent clinical experiences and opinions. Not until then will it be possible to evaluate correctly the use of the drug in the treatment of gonorrhea. We fear that the unwarranted publicity from pharmaceutical concerns, which is deluging the physicians of the country, may prove so enticing that many practitioners will succumb to these optimistic and alluring statements and not give the careful scientific thought to this new drug that is demanded.

When optimism takes precedence over scientific effort, the scientist is left out of the experiment. The physician should be more analytical of himself and his actions. There is hardly a doubt that we are regressing in our scientific concept of gonor-

rhea and its cure when we permit the glowing but unproved statements in leaflets of chemical concerns to make us cast aside time-honored and reliable measures for something which is said to be newer and surer. "The greater the ignorance, the greater the dogmatism." There is not a physician in this country who would not welcome the day that a true gonococcocide is discovered!

SERUM-PROTEIN STUDIES IN HYPERTHYROIDISM

ELMER C. BARTELS, M.D.*

BOSTON

THE present study of the serum proteins in hyperthyroidism was undertaken because of conflicting reports in the current literature, and in order to obtain additional information regarding the disturbances in general body metabolism in this disease.

Di Benedetto[1] (1933) made a comparative study in 15 normal women and 15 women who had hyperthyroidism and whose basal metabolic rates were more than plus 20 per cent. In cases of hyperthyroidism the value for total protein did not vary from normal, the serum-albumin content was increased a little, the globulin content was increased a little more than the serum albumin, and the albumin-globulin ratio was elevated. He reported that these results were similar to those observed in a dog with hyperthyroidism produced experimentally by the ingestion of thyroid substance. No constant parallelism was found between the variation of the metabolism and the serum-protein content.

Olivetti and Bobbio[2] studied the proteins of the blood in individuals suffering from disease of the thyroid gland. They reported a tendency to hypoproteinemia with lowering of the albumin-globulin ratio in cases of hyperthyroidism. They attributed this alteration in the value for proteins to a specific influence of the thyroid gland on the regulation of the body-protein mixtures through the neuroendocrine system.

Labbé, Nepveux and Ornstein[3] (1932) reviewed the literature and found conflicting reports. An increase in the total protein content was noted by some observers, changes in the albumin-globulin ratio with an unchanged value for total protein by others, and entirely normal conditions by still others. The study made by Labbé, Nepveux and Ornstein revealed no deviation from the normal. No relation was found between the values for the proteins and the severity of the disease as evidenced by the basal metabolic rate.

Another reason for the present study was to obtain further evidence of changes in hepatic function in hyperthyroidism. Sufficient clinical and pathological evidence is at hand to indicate that the liver undergoes changes in this disease,[4, 5, 6, 7, 8, 9] and in recent articles significant changes in the serum-protein content in diseases of the liver have been reported. Tumen and Bockus,[10] in a recent report of the changes in the value for the serum proteins in hepatic disease, corroborated the work of most other observers, who showed a lowering of the serum-albumin content with an elevation of the serum-globulin content and a reversal of the albumin-globulin ratio in this condition. The lowering of the value for serum albumin was the most consistent change noted; elevation in the serum-globulin content and lowering of the albumin-globulin ratio occurred, but were not so constant or significant as the former. This change in the value for serum proteins was thought to be due to alteration in the function of the liver, either in the manufacture of albumin or in the maintenance of its proper level in the blood.

Snell,[11] in a recent editorial on the subject of the serum proteins in hepatic disease, asserted that evidence at hand indicated the liver was responsible for the reduction in the plasma proteins, particularly serum albumin. He reviewed experimental evidence that the liver figures strongly in the maintenance of stored and circulating protein. In considering the diagnostic and prognostic significance of the level of the plasma proteins, he concluded that a reversible reaction is apparently possible, since with recovery in the liver the protein content of the serum returns to normal.

MATERIAL

Determination of the serum-protein content by the micro-Kjeldahl method was carried out in 59 cases of hyperthyroidism which exhibited a wide range of toxicity. In 31 cases (Table 1) the level of the total protein was determined on three occasions — on admission to the hospital, just before operation (after a preoperative course of treatment, usually of ten days' duration) and three months after operation, when the usual postoperative determination of the metabolic rate is made. The

From the Medical Department, Lahey Clinic, Boston.
*Physician, Department of Internal Medicine, Lahey Clinic.

Table 1. *Summary of Cases Studied on Admission, Preoperatively and Postoperatively.*

Case No.	Sex	Age	Duration of Disease	Weight Loss	ON ADMISSION						PREOPERATIVE						POSTOPERATIVE					
					Basal Metabolic Rate	Hippuric Acid	Proteins				Basal Metabolic Rate	Hippuric Acid	Proteins				Basal Metabolic Rate	Hippuric Acid	Proteins			
							Albumin	Globulin	Total	Albumin-Globulin Ratio			Albumin	Globulin	Total	Albumin-Globulin Ratio			Albumin	Globulin	Total	Albumin-Globulin Ratio	Number of Operations
		yr.	mo.	lb.	%	gm.	gm. per 100 cc.	gm. per 100 cc.	gm. per 100 cc.		%	gm.	gm. per 100 cc.	gm. per 100 cc.	gm. per 100 cc.		%	gm.	gm. per 100 cc.	gm. per 100 cc.	gm. per 100 cc.		
1	F	30	2	20	+49	2.16			6.3		+21	2.84			6.0		+8				7.9		1
2	F	39	12	12	+17	2.83	3.6	3.15	6.8	1.1	+17	2.94	3.29	3.25	6.6	1.0	+5	3.13			8.8		1
3*	F	52	24	15	+40	0.89	3.9	2.3	6.3	1.7	+28	1.97	4.1	2.4	6.6	1.6	—4	3.03			8.7		1
4	M	21	12	10	+53	2.36	3.6	3.6	7.3	1.0	+35	2.96			8.2	1.0	—6	3.09	5.3	1.9	7.3	2.6	2
5	F	32	5	19	+26	2.45			6.3		+16	2.88	3.5	3.0	6.6	1.0	—8	3.01			7.5		1
6	F	36	6	17	+44	1.35			5.3		+38	2.26			5.4		—16	3.16			7.0		2
7	F	55	48	80	+21	1.49	4.0	2.0	6.0	2.0	+17	1.22	3.9	3.6	7.5	1.0	—10		4.5	3.4	8.0	1.3	2
8	F	33	1.5	20	+54	1.69	4.3	1.9	6.1	2.0	+28	2.08	5.1	2.0	7.1	2.5	—3		5.3	1.8	7.4	2.9	2
9	F	27	24	None	+76	2.31			6.4		+51	2.79	3.0	3.0	6.1	1.0	+5	3.0			8.0		2
10	F	25	12	9	+68	2.50			5.7								+2	3.02			9.0		2
11	F	22	2	None	+18	2.62	3.2	2.8	6.1	1.1							—5	3.97			7.8		1
12	F	32	5	10	+44	1.07			6.4		+19	2.32			7.6		—15	3.27			8.2		1
13	F	62	4	20	+32	2.18			5.5		+37				6.8		—6	3.08			7.8		2
14*	F	61	36	20	+44	2.11			6.4		+27	2.01			6.8		—3	3.10			7.3		1
15	F	55	4	32	+66	1.65			6.3		+32	2.60			4.9		—14				8.0		2
16	F	48	8	30	+30				6.8		+16	2.75					—19	4.61			7.2		1
17	F	36	1	29	+32	1.70			6.0		+24	1.62			6.7		—13	2.16			7.9		1
18	F	46	8	20	+26	1.98			6.8		+16	1.26			6.4		—5				8.2		2
19	F	46	3	20	+56	1.28			5.8								+3				6.8		2
20	F	46	48	3	+44	2.54	4.1	2.80	6.9	1.4							—15		4.1	3.6	7.7	1.1	2
21	F	43	30	22	+53	2.07	4.4	2.6	7.0	1.7	+52	3.02	4.5	2.0	6.5	2.2	—10				8.7		2
22	F	39	8	30	+90	3.20					+ 6	3.14	4.0	2.0	6.1	1.86	+6				7.7		2
23	F	53	3	21	+56		2.6	3.1	5.7	0.9	+33				5.3		—7	2.70			6.6		2
24	F	34	10	20	+67	3.10			5.8		+34	2.99			7.7		—13	3.0			7.6		2
25	F	32	12	7	+22				7.5		+19				6.7		—4				8.6		1
26	M	57	24	15	+36	1.71			5.7								+7	3.12			7.2		1
27*	M	59	6	None	+24										5.4		+14				8.7		2
28*	F	43	12	None	+43	2.33	4.3	2.1	6.4	2.0	+37	2.71	4.6	1.9	6.6	2.3	—10	3.43			9.8		1
29	F	54	24	None	+43				7.2		+19				6.6		—5				7.5		1
30	F	31	6	8	+44		2.6	3.6	6.1	0.7	+29		3.0	2.6	5.7	1.1	—12		5.1	1.7	6.8	3.0	2
31	F	28	8	25	+80				5.0		+50				6.9		—8				7.4		2

*Adenomatous goiter.

Table 2. *Summary of Cases Studied on Admission and Preoperatively.*

Case No.	Sex	Age	Duration of Disease	Weight Loss	ADMISSION STUDIES						PREOPERATIVE STUDIES						Number of Operations
					Basal Metabolic Rate	Hippuric Acid	Proteins			Albumin-Globulin Ratio	Basal Metabolic Rate	Hippuric Acid	Proteins			Albumin-Globulin Ratio	
							Albumin	Globulin	Total				Albumin	Globulin	Total		
		yr.	mo.	lb.	%	gm.	gm. per 100 cc.	gm. per 100 cc.	gm. per 100 cc.		%	gm.	gm. per 100 cc.	gm. per 100 cc.	gm. per 100 cc.		
1	F	20	8	13	+98	0.92	3.0	2.9	6.0	1.1	+55	1.37	3.2	3.3	6.5	0.9	2
2	F	16	12	14	+33	1.42	3.5	2.7	6.2	1.3	— 4	1.45	4.3	2.5	6.8	1.7	2
3*	F	66	72	20	+28	0.54	3.8	1.3	5.2	2.8	+10	0.67	3.8	2.3	6.0	1.6	2
4*	F	52	36	None	+46	1.46	4.7	2.4	7.2	1.5	+32	2.57	4.7	2.4	7.1	1.9	2
5*	F	57	12	15	+40	2.11	3.9	3.2	7.1	1.1	+38	1.79	4.5	3.1	7.7	1.4	2
6*	F	63	4	26	+50		3.7	2.3	6.0	1.6	+37	2.45	4.1	3.5	7.6	1.0	1
7*	M	45	5	15	+54	2.89			5.8		+39	2.99	3.9	1.9	5.9	1.9	1
8*	F	60	24	10	+21	1.97			4.9		+11	1.79	4.1	2.3	6.4	1.7	1
9	M	29	12	35	+48	1.48			7.1		+29				7.3		2
10	F	45	10	None	+49	0.94			5.5		+30	2.90			7.8		1
11	F	37	24	None	+41	2.22			7.6		+31	1.92			6.6	1.3	1
12	F	32	10	35	+47	0.93			6.7		+30	1.72			7.0		2
13	F	31	18	None	+88	1.44			6.9		+55	2.93			5.6		2
14	F	29	5	26	+48				6.5		+29				7.1		2
15	M	39	18	None	+19	2.37			8.3								1
16	M	62	6	71	+80	2.64			7.2		+65	3.04	3.2	3.6	6.9	0.88	2
17*	F	47	18	17	+33	2.30	2.9	3.0	6.1	0.9							2
18	F	54	24	30	+29	2.39			5.2								2
19	M	54	14	50	+63	2.24			6.5								2
20	F	31	5	4	+46	1.75			6.2		+25	2.49			6.5		1
21*	F	53	4	12	+51	1.93			6.5		+28	2.51			6.9		1
22*	F	33	6	10	+17	2.26			7.4								1
23*	F	30	36	30	+39	2.31			6.7		+15	2.79			6.7		1
24	M	44	2	40	+34	2.65			5.8								2
25*	F	64	7	12	+28				7.3		+ 6				6.2		1
26	F	38	12	70	+72		2.7	2.9	5.8	0.9	+35				6.9		2
27	M	37	24	50	+45				7.5		+20				5.4		1
28	F	63	12	42	+66				6.7		+26				6.7		2

*Adenomatous goiter.

serum-albumin and serum-globulin contents also were determined separately on admission in 11 cases, just before operation in 10 cases and three months after operation in 5 cases. In an additional group of 28 cases (Table 2) the total serum-protein content was obtained on admission and before operation, but not after operation. The serum-albumin and serum-globulin contents were determined separately on admission in 8 cases and preoperatively in 9. The determination of the serum

RESULTS

The average total protein content determined on admission to hospital in 43 cases of primary hyperthyroidism was 6.3 gm. for each 100 cc. of serum; in 14 cases of adenomatous goiter the value was the same. The effect of hyperthyroidism on the total serum-protein content is apparently the same in both types of disorder.

The distribution of cases and the range of determinations of the total serum-protein content

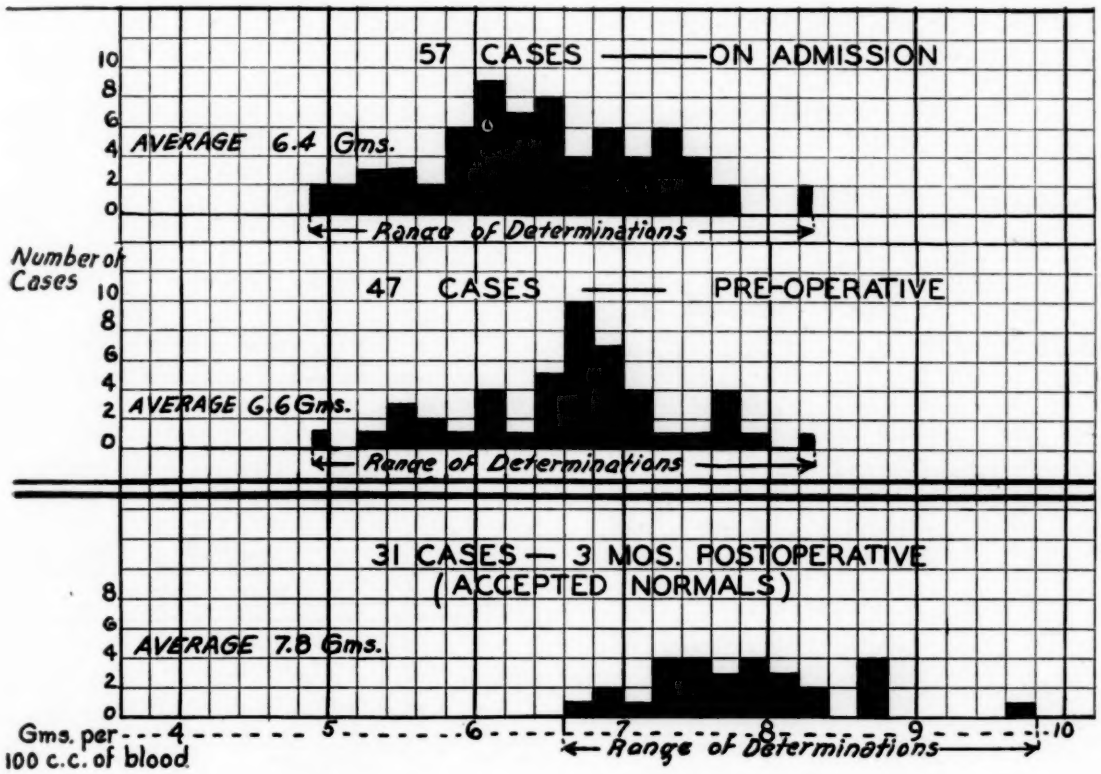


Figure 1. *Total serum-protein content.*

proteins on examination three months after operation (Table 1) may be considered to represent a control series, since by this time the patients had regained their health and the basal metabolic rate had returned to normal. That this assumption is correct is also shown by the fact that the determinations made at this time were well within the range of normal according to laboratory standards.

A study of the hepatic function by means of the excretion test of hippuric acid by the method of Quick[12, 13] was carried out in most of the cases in this series, as indicated in Tables 1 and 2. This procedure permitted a comparison of two observations relating to the condition of the liver in the cases studied.

on admission, immediately before operation and three months after operation are shown in Figure 1. It should be remembered that the determinations made three months after operation were carried out at a time when the patients had recovered from the disease and were considered normal. The average level for total serum protein on admission was 6.4 gm. for each 100 cc., with a range of from 4.9 to 8.3 gm. In 63 per cent of the cases the values for the total serum proteins were below 6.6 gm., which is the lowest level in the normal range. In only 1 case was the level for total serum protein above the average normal of 7.8 gm.

The determinations made after the ten-day preoperative preparation showed that little change had taken place during this period. The average

value was 6.6 gm., and the range of determinations remained the same. An increase in total serum protein content occurred in 47 cases, however, and at this time in only 37 per cent were the determinations below 6.6 gm.

Three months after operation the range of the total serum-protein determinations in 31 cases was found to be between 6.6 and 8.8 gm., with an average of 7.8 gm. — a normal variation and an average value.

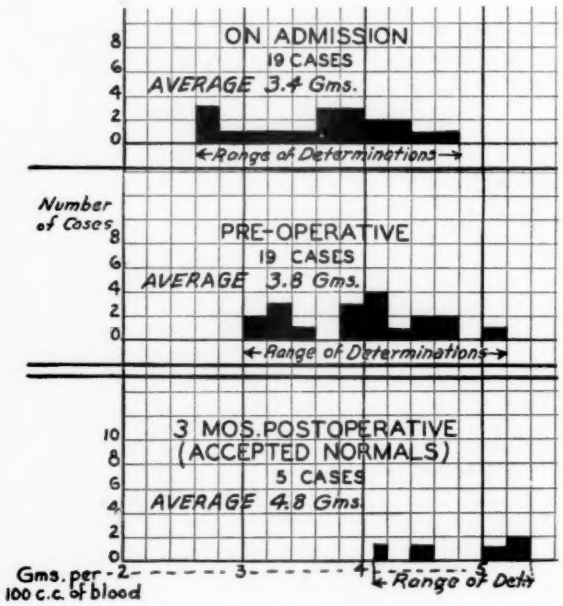


Figure 2. *Serum-albumin content.*

The serum-albumin (Fig. 2) on admission ranged between 2.6 and 4.7 gm., with an average of 3.4 gm. for each 100 cc. In 73 per cent (14) of 19 cases the determinations were below 4.1 gm., the lowest figure in the normal range. Before operation the average serum-albumin content was 3.8 gm., with a range of from 3 to 5.1 gm.

At this point in only 52 per cent (10 of 19 cases) were the determinations below the accepted normal value. The average serum-albumin content three months after operation was 4.8 gm., with a range of from 4.1 to 5.3 gm.

The average serum-globulin content (Fig. 3) was found to be practically the same on admission, before operation and three months after operation. The figures were 2.6, 2.6 and 2.5 gm., respectively. With one exception the range also remained the same in the three instances. A single determination made on admission was 1.3, compared to the lowest normal of 1.7 gm.

The average albumin-globulin ratios, expressed as the figure obtained by dividing the amount of albumin by that of globulin, were 1.4 and 1.5, respectively, on admission and before operation as compared to the normal average of 2.2 (Fig. 4). Hence, the range was reduced on admission and preoperatively; the low figure on admission was 0.8.

No parallelism was found between the level of the serum proteins and the duration of the hyperthyroidism or the amount of weight lost during the course of the disease. In patients who had had hyperthyroidism for only a few months, the levels for proteins were as low as in those who had had it for years. As for the relation of serum-protein content to loss of weight, the patient who had the highest total serum-protein content — 8.3 gm. — had not lost weight; on the other hand, the patient with the lowest protein — 4.9 gm. — had lost only 10 lb.

No relation was found between the level of the total serum protein and the degree of elevation

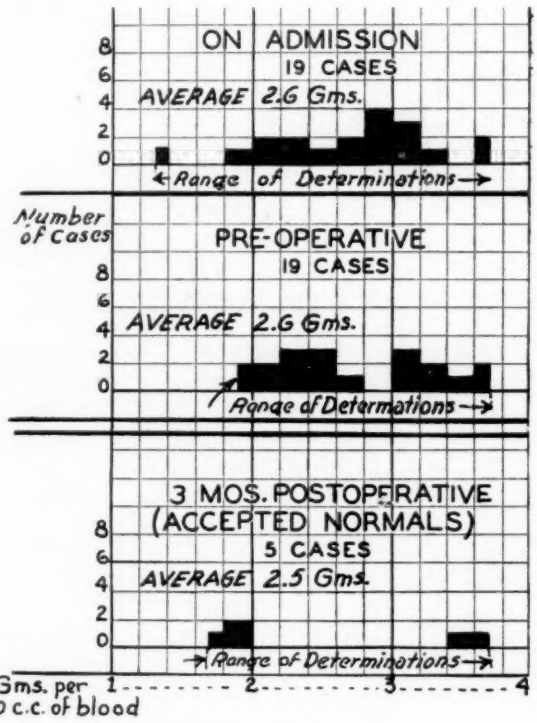


Figure 3. *Serum-globulin content.*

of the basal metabolic rate. But in comparing these two factors certain features were noted. In some of the cases of severe adenomatous goiter the basal metabolic rate was only slightly elevated and the total serum-protein content was moderately low. It has nevertheless been recognized that the basal metabolic rate in cases of adenomatous goiter with hyperthyroidism does not always indicate the degree of toxicity, as it does in primary hyperthyroidism. Again, of the 3 patients in whom the value for the total serum proteins was only slightly reduced and the basal metabolic rates were high, — more than plus 70, — 2 had

not lost weight and 1 had diabetes mellitus as a complicating factor. It has been recorded in a recent paper[14] that the hepatic function is not greatly disturbed in cases of hyperthyroidism which are complicated by the presence of diabetes.

The excretion test of hippuric acid by the method of Quick has received considerable clinical trial as a means of determining the functional capacity of the liver, and has proved satisfactory. Since

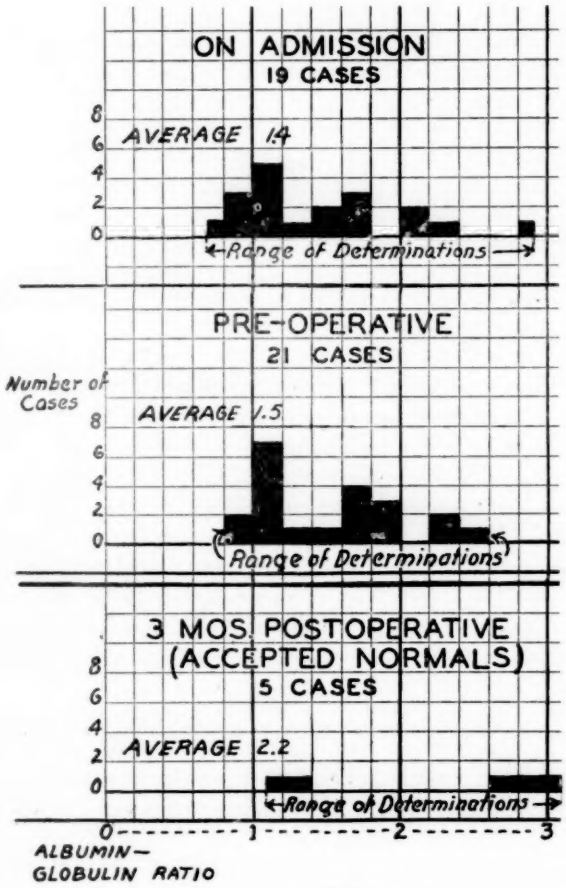


Figure 4. *Albumin-globulin ratio.*

the levels for the serum proteins gave information as to the condition of the liver, it was suspected that there might be a corresponding change in the two tests. It was found that the relation was only approximate. In 12 cases of hyperthyroidism in which the values for total serum proteins were below 6 gm. per 100 cc., the value for excretion of hippuric acid was 1.95 gm., as compared with 9 cases in which the total serum-protein content was more than 7 gm. and the average excretion of hippuric acid was only slightly greater, 2.11 gm.* This failure to demonstrate a direct relation is difficult to explain. It may be, of course, that each test determines a specific type of hepatic function, and that excretion test of hippuric acid is an index to the function concerned with carbohydrate metabolism (glycogenic function), while the level of serum protein is an index to the function concerned with protein metabolism (proteogenic function).

*The normal value for the excretion of hippuric acid is approximately 3 gm.

RELATION OF SERUM-PROTEIN LEVEL TO SEVERITY OF HYPERTHYROIDISM

When study of a case of hyperthyroidism shows unusual severity of the disease, subtotal thyroidectomy should be performed in two stages rather than in one. As this decision is of utmost importance to the patient and is conditioned by the clinician's opinion a further search for some criterion was carried out by comparing the level of the total serum proteins on admission with the type of surgical procedure performed. In Figure 5 it is shown that of the 25 cases in which

NUMBER OF CASES	TYPE OF OPERATION	AVERAGE SERUM PROTEIN IN MGS.	NUMBER OF CASES HAVING TOTAL SERUM PROTEIN BELOW 6 MGS.
25	SUBTOTAL THYROIDECTOMY	6.5	4 (16%)
32	HEMI-THYROIDECTOMY	6.2	11 (34%)

Figure 5. *Serum-protein content in cases in which subtotal thyroidectomy or hemithyroidectomy was carried out.*

hyperthyroidism was sufficiently mild clinically to permit subtotal thyroidectomy, the average total serum-protein content was 6.5 gm. per 100 cc. In only 4 cases, or 16 per cent, was the total protein content less than 6 gm. In 32 cases in which the hyperthyroidism was of sufficient severity to require a hemithyroidectomy as the first operation, the average value for total serum protein was 6.2 gm. per 100 cc.; in 11 of these cases, or 34 per cent, the total serum-protein content was less than 6 gm. Again, of the 15 cases in which the total protein content was less than 6 gm., hemithyroidectomy was done in 73 per cent. This indicates a direct relation between the clinical severity of the hyperthyroidism and the level of the total serum protein.

In 5 cases (Table 1, Cases 23 and 30; Table 2, Cases 1, 17 and 26) the serum-albumin content was 3 gm. or less, the lowest total being 2.6 gm. Primary hyperthyroidism was present in 4 cases, adenomatous goiter with hyperthyroidism in 1, and in all 5 cases two operations were performed. The average basal metabolic rate in these cases was plus 61 per cent; plus 44 was the average for the entire series. The average values for total serum

protein, serum globulin and the albumin-globulin ratio were 5.9 gm., 3.1 gm. and 0.9, respectively. This lowering in the serum-albumin content with slight elevation of the level for serum globulin and reduction of the albumin-globulin ratio indicates what a marked alteration may occur in the serum-protein content in cases in which severe grades of hyperthyroidism are present.

SUMMARY

Analysis of the data presented indicates that marked alterations occur in the serum-protein content of cases with clinical hyperthyroidism. In this series the average value for total serum protein was 6.4 gm. per 100 cc. on admission to the hospital; in 63 per cent of the cases the determinations were below the normal range. Improvement occurred after ten days of preoperative treatment, when the determinations were below normal in only 37 per cent. Three months after operation in all cases the value for the total serum protein was normal. The serum-albumin content in 73 per cent of cases was below normal on admission, the average being 3.4 gm. Preoperatively, the serum-albumin content was below normal in 53 per cent, with an average of 3.8 gm., and in all cases it was normal three months after operation. No apparent change from normal was noted in the serum-globulin content on admission, and preoperatively the average albumin-globulin ratio was reduced to 1.4; three months after operation it was 2.2, a normal ratio.

No direct relation was found between the level of the serum proteins and duration of hyperthyroidism, basal metabolic rate, amount of weight loss or type of hyperthyroidism. A rough correlation was found between the level of the total serum protein and the excretion of hippuric acid, used as a test of hepatic function.

A relation was found to exist between the level of the total serum protein and the severity of hyperthyroidism, as indicated by clinical opinion as to the need for a one-stage or a two-stage operation. In 73 per cent of the cases in which the value for the total serum proteins was below 6 gm., a two-stage operation was required. Furthermore, in all cases in which the serum-albumin content was 3 gm. or less, two-stage operations were required.

The changes noted in the serum proteins may be attributed to disturbances in the function of the liver. Changes in structure and in the function of the liver have been noted in cases of hyperthyroidism, and the protein disturbance may be accepted as further evidence of this hepatic change. It is unlikely that the alteration in serum protein is on a nutritional basis, since patients with hyperthyroidism usually eat more food of all kinds than do normal individuals. In hyperthyroidism an increase in the blood volume is found, this being attributed to an increase in the body's need for oxygen. Such a change might be said to produce the lowering of the serum proteins, but this does not seem likely inasmuch as there are parallel increases in both the plasma and cells, as evidenced by normal hematocrit values.

This deviation of serum-protein content from normal may have physiological effects on the body as a whole. It may be responsible for the edema in cases of hyperthyroidism that is not caused by cardiac or renal insufficiency, since in some of these cases the total serum-protein content fell below the critical level. There is a possible relation between serum-protein content and postoperative thyroid crisis.

On the basis of the changes in the values for serum proteins in hyperthyroidism, a part of the preoperative treatment of this disease should perhaps be a high-protein diet. It is admitted that failure has been reported in attempts to alter the serum proteins in cases of cirrhosis of the liver by giving a diet high in protein; in hyperthyroidism, however, a functional rather than a fixed pathologic condition exists, as is evidenced by a return to normal in the serum proteins three months after operation.

REFERENCES

1. Di Benedetto, E. J.: Viscosité et équilibre protéique du sérum dans l'hyperthyroïdisme humain. Comp. rend. Soc. de biol. 113:452-453, 1933.
2. Olivetti, R., and Bobbio, A.: La proteinemia nella disfunzioni tiroidee. Minerva med. 2:439-446, 1935.
3. Labbé, M.; Nepveux, F., and Ornstein, I.: Les albumines du sérum sanguin dans la maladie de Basedow et les états d'hyperthyroïdie. Rev. franç. d'endocrinol. 10:97-104, 1932.
4. Cameron, G. R., and Karunaratne, W. A. E.: Liver changes in exophthalmic goitre. J. Path. & Bact. 41:267-282, 1935.
5. Beaver, D. C., and Pemberton, J. deJ.: The pathologic anatomy of the liver in exophthalmic goiter. Ann. Int. Med. 7:687-708, 1933.
6. Youmans, J. B., and Warfield, L. M.: Liver injury in thyrotoxicosis as evidenced by decreased functional efficiency. Arch. Int. Med. 37:1-17, 1926.
7. Lichtman, S. S.: Liver function in hyperthyroidism. *Ibid.* 50:721-729, 1932.
8. Maddock, W. G.; Coller, F. A., and Pedersen, S.: Thyroid crisis: its relation to liver function and adrenalin. West. J. Surg. 44:513-521, 1936.
9. Bartels, E. C., and Perkin, H. J.: Liver function in hyperthyroidism as determined by the hippuric acid test. New Eng. J. Med. 216:1051-1060, 1937.
10. Tumen, H., and Bockus, H. L.: The clinical significance of serum proteins in hepatic diseases compared with other liver function tests. Am. J. M. Sc. 193:788-800, 1937.
11. Snell, A. M.: The plasma proteins and liver disease. Am. J. Digest. Dis. & Nutrition 4:258-259, 1937.
12. Quick, A. J.: The synthesis of hippuric acid: a new test of liver function. Am. J. M. Sc. 185:630-635, 1933.
13. *Idem*: Clinical value of test for hippuric acid in cases of disease of the liver. Arch. Int. Med. 57:544-556, 1936.
14. Bartels, E. C.: Liver function in hyperthyroidism as determined by the hippuric acid test. Ann. Int. Med. (in press).

A CASE OF HEMOCHROMATOSIS WITH DEGENERATION OF THE HEART MUSCLE AND DEATH FROM CONGESTIVE HEART FAILURE

GEORGE BLUMER, M.D.,* AND ROBERT R. NESBIT, M.D.†

NEW HAVEN, CONNECTICUT

THE peculiar disturbance of pigmentary metabolism known as hemochromatosis usually gives rise to the clinical picture of bronzed diabetes with hepatic cirrhosis, because the process affects preponderantly the pancreas, liver and skin. While the heart muscle is involved in the process in 50 per cent of the cases, and while in many of these there is undoubtedly a certain amount of damage to the cardiac musculature, only rarely is this damage sufficient to lead to pronounced cardiac failure. In the case here presented this complication did occur. The patient was on the service of Dr. William F. Collins, to whom we are indebted for the opportunity to examine the patient and report the case.

CASE REPORT

J. C. B., a retired plumbing contractor 54 years of age, a widower and a native of the United States, was admitted to Hospital of St. Raphael, January 7, 1937. His chief complaint on entrance was cough, and swelling of the entire body. He had been in fairly good health until about a year before admission. At this time he developed a short, nonproductive cough which was especially bad at night. About 9 weeks before admission this cough became worse, though still nonproductive, and sleeplessness and orthopnea developed. There was some substernal pain, which disturbed the patient but was never very severe. About 8 weeks before admission swelling of the feet and ankles was noted; this gradually spread until it involved the subcutaneous tissue of the entire body. During this time the urine was scanty, but the patient had no dysuria or hematuria. He had had no indigestion, and the bowels were normal. There was no loss of weight. For the preceding 2 years he had noticed a scaly condition of the skin, with brownish discoloration.

There was nothing significant in the family history except that the patient's father died at 72 of acute cardiac failure. His earlier history was noncontributory. He was at one time a plumber, but for many years had been a plumbing contractor, so that lead poisoning was improbable; there was no history of exposure to copper. He had been unusually healthy most of his life.

Physical examination showed a well-developed man. The face was puffy, and there was generalized edema all over the surface of the body. The breath was urinous. The tonsils were atrophic. The tongue was clean and moist. There was dulness to flatness at the bases of both lungs posteriorly, especially on the right side, with absence of tactile and vocal fremitus. Moist rales were heard over the upper parts of both lungs. The heart appeared to be somewhat enlarged to the left. The sounds were of only fair quality; there was a systolic murmur with its maximum over the lower end of the sternum, which was heard also along the right sternal margin. The blood pressure was 132/102. The abdomen was protuberant, there was dulness in the flanks, and the abdominal organs could not be palpated. There was moderate pitting edema of the extremities. The skin was dry and showed a bronzed pigmentation.

Dr. Collins's note on January 6, the day before admission, confirmed these findings. He noted that the patient was apathetic, that the thyroid appeared to be slightly enlarged, that the heart was considerably enlarged and the sounds rather feeble, that the abdomen was tender, especially in the right upper quadrant, and that the skin was dry, scaly and deeply pigmented. At this time 400 cc. of clear fluid was removed from the right chest.

On January 19 the patient was seen by one of us (G. B.) in consultation. It was noted that there was pigmentation of the skin involving the entire trunk, the arms, face and legs, especially the upper part of the thighs. The pigmentation was brown but was not uniform. There were areas of less pigmented skin scattered over the body between areas of more deeply pigmented skin. There were small patches of slightly pigmented mucous membrane on the inner aspects of both cheeks. There was marked gingivitis, but no lead or bismuth line. The neck veins were prominent, there was cyanosis of the ears and lips, there were signs of fluid in both pleural cavities, and there was a fair amount of moisture at the lower parts of both lungs. The cardiac impulse was feeble, diffuse and in the fifth space, 9.5 cm. to the left of the median line. The first sound was of poor quality and the sounds at the base were very feeble. The pulse was regular in rate but was small and easily compressible. The abdomen was distended and dull in the flanks, and the abdominal organs could not be palpated on account of this distention. There was marked edema of the genitalia, and marked pitting edema of the legs and thighs. The patient had no fever.

The urine had a specific gravity of 1.020; it contained a slight trace of albumin and of sugar, but microscopically only urates. The basal metabolic rate was —23 per cent. The hemoglobin varied from 80 per cent on admission to 70 per cent, 10 days later. The red-blood-cell count was 5,000,000 on admission and fell to 4,400,000, 10 days later. The leukocytes numbered 12,800 on admission and 18,600, 10 days later, with polymorphonuclears 75 and 81 per cent respectively, the remaining cells being lymphocytes. The fluid from the chest showed no organisms; smears and cultures were negative. The nonprotein nitrogen on two occasions was 48 mg. per cent. The blood Kahn reaction was negative. The blood sugar was 140 mg. per cent on admission, and 200 mg. 10 days later.

The patient gradually failed, and died on January 30.

It was noted that the main difficulty was circulatory, that the man was suffering from pronounced congestive heart failure, which did not respond to ordinary methods of treatment, and that the history of substernal pain suggested the possibility of coronary-artery disease. It was thought that the congestive failure was caused by arteriosclerotic heart disease. This diagnosis did not of course explain the pigmentation; in the discussion of this

From the Medical and Pathological services of the Hospital of St. Raphael, New Haven, Connecticut.

*Consulting physician, Hospital of St. Raphael.

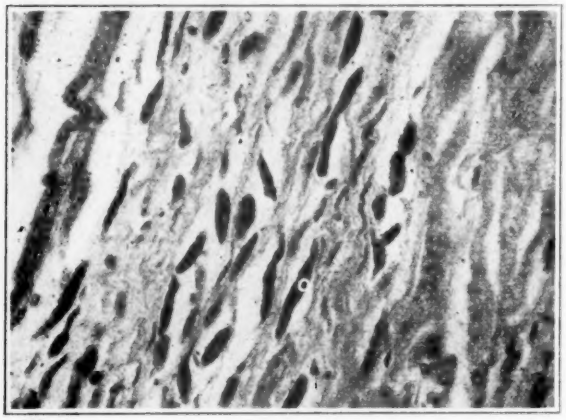
†Pathologist, Hospital of St. Raphael.

it was pointed out that the blood pressure made the diagnosis of Addison's disease extremely unlikely, and that a diagnosis of hemochromatosis was indicated, especially in view of the trace of sugar in the urine and the high blood-sugar content.

The autopsy was performed by one of us (R. R. N.) on January 30. The important anatomical diagnoses and the chief items of interest in the gross and microscopic examinations of the organs mainly affected by the disease follow.

"*Anatomical Diagnoses:* hemochromatosis of the spleen, pancreas, liver, skin, thyroid gland and lymph nodes; hemochromatosis of the heart with marked fibrosis; cirrhosis of the spleen and liver; cardiac mural thrombi; acute pulmonary and visceral congestion with pulmonary hemorrhage; pericardial and bilateral pleural effusion; ascites; generalized pitting edema; chronic passive congestion of the viscera; early arteriosclerosis.

"The *heart* weighs 410 gm. The pericardial surface is smooth. There is a very noticeable brown pigmentation. The coronary arteries are moderately thickened, but there are no demonstrable occlusions. The coronary veins are congested and dilated. The myocardium is rather soft and flabby. On section, the myocardium is deep-brown and shows intense streaking and scarring, also noticeably brown. The right side of the heart is markedly dilated. In the right auricular appendage is a large, well-organized, adherent gray-red clot. There is a similar clot in the left auricular appendage. The remainder of the endocardium is smooth, and the valves are all free and appear functionally normal. No vegetations are demonstrable.



Heart Muscle (enlarged from 400 ×; G and H filters; phosphotungstic acid and hematoxylin stain). The pigment infiltration, the fractionating of myofibrils and connective-tissue proliferation are shown. In the outer edges, on either side, are shown fibrils which still retain some of their cross striations, although the pigment granules are seen within the fibrils; in the center the complete replacement of fibrils by pigment and their massive destruction are well demonstrated.

"Microscopic examination shows that the epicardial fat is normal. The coronary arteries show a slight intimal proliferation without any medial changes; no vessel can be found in any section which is appreciably diminished in caliber. The myocardium is characterized by an intense pigment infiltration of the myofibrils, with degeneration and replacement fibrosis. This pigment gives a positive iron reaction. The myofibrils show varying degrees of degeneration, some with slight loss of cross striations and varying degrees of pyknosis of the nuclei, others with marked fragmentation and dropped nuclei, while practically all show some degree of irregularity of staining. In some instances large deposits of pigment are laid down in lines, apparently within the sheath of the fibrils, while in other foci clumps of pigment granules lie within a fibroblastic mesh, in which may be seen occasional mononuclear phagocytes containing engulfed pigment. The endocardium of the auricle and the auricular appendage is covered by a thrombus, some of which is organized and shows fibroblastic proliferation, while the remainder shows a more recent process in which fairly well preserved erythrocytes are still visible, as compared to the almost completely degenerated cells in the older portions. The veins throughout the sections are intensely dilated by closely packed red cells.

"The *spleen* weighs 210 gm. The capsule is smooth and dark. The organ is very firm, and on section imparts a gritty feeling through the knife. The cut surface is purplish red, due to congestion, and shows apparent increase of fibrous stroma.

"Microscopic examination shows nothing of note in the capsule. The sinusoids are widely distended by red cells and many mononuclear phagocytes containing engulfed debris and pigment. The endothelial lining cells are in almost all instances loaded with iron-positive pigment, so that some of these cells appear triple their normal size. The lymphoid follicles are obscured by the intense congestion, but otherwise are normal. The arteries show a slight intimal proliferation, more marked than that observed in the heart. The veins are intensely engorged with red cells.

"The *pancreas* weighs 130 gm. It is a deep mahogany brown. It is firm, and on section this color is present throughout its entire structure. There is no evidence of hemorrhage.

"Microscopic examination shows that the sections of pancreas are essentially brown. Almost all the acinar cells and those of the islets are filled with iron-positive pigment, and the whole islets and large groups of acinar cells are completely degenerated with pyknotic or dropped nuclei. Between the lobules and also in the intra-acinar spaces there is a marked fatty infiltration throughout the sections, while others show focal fibroblastic proliferation replacing portions of the lobules. In this tissue are numerous mononuclear phagocytes with engulfed pigment, and also clumps of pigment, lying free. The islets throughout are seen to be more seriously involved by the pigment infiltration than are the acinar cells. The ducts of the pancreas show desquamation of epithelium, but are otherwise normal. The arteries show a moderate intimal proliferation, and the veins are intensely engorged with red cells.

"The *liver* weighs 2150 gm. The capsule is smooth but irregular, because of changes in the hepatic structures beneath. The organ is intensely brown. On section, a definite gritty feeling is imparted through the knife. A large amount of dark blood oozes from the cut surface. When this is scraped away, an increase of intense brown fibrous tissue is seen, and the hepatic tissue is markedly diminished and is a very deep brown. This increase in fibrous tissue appears to outline the periphery of the lobules of the liver. The veins are markedly congested and dilated. Grossly, the biliary system and gall bladder are not remarkable.

"Microscopic examination shows that the sections, like those of the pancreas, are mainly brown. There is an intense peripheral fibroblastic proliferation, in which there is evidence of bile-duct proliferation. The fibrous tissue

and the bile-duct cells are both loaded with iron-containing pigment which, in the fibrous tissue, is present in free clumps and also in the mononuclear phagocytes. The bile-duct cells show marked degeneration with pyknotic and dropped nuclei as a result of the pigment infiltration. The fibrous tissue contains isolated small groups of parenchymal cells, which are likewise loaded with pigment. The parenchymal cells almost without exception contain varying amounts of pigment infiltration. In some instances there are whole clumps of cells in which nuclei are not demonstrable, or else are pyknotic. The cytoplasm is very coarsely granular and stains irregularly. The sinusoids are widely dilated and filled with closely packed red cells, and the central veins show similar processes. The Kupffer cells in many instances show marked phagocytosis of pigment.

"All the *lymph nodes* examined, including those of the mediastinum, the upper and lower abdomen and the pelvis, are enlarged and very deep brown. The brown color is universally distributed through their substance. The nodes of the mediastinum are much more markedly swollen than those elsewhere, and are soft and boggy.

"Microscopic examination shows an intense iron-containing pigmentation, the pigment lying free or in the cytoplasm of phagocytes which fill the sinusoids. There is moderate hyperplasia of the lymphoid follicles.

"The *thyroid* is a very deep brown, and on section this color is distributed throughout the gland. The colloid is diminished, and the gland is small and contracted. There is apparently an increase in the fibrous tissue.

"Microscopic examination shows an intense pigmentation of the acinar cells with varying degrees of degeneration, but complete in numerous instances. Entire alveoli are frequently replaced by cell membranes containing large clumps of iron-positive pigment. There is a marked proliferation of fibroblasts surrounding the alveoli, and in this fibroblastic tissue there is a very prominent lymphoid infiltration. Large numbers of mononuclear phagocytes filled with pigment are seen. The colloid is greatly reduced in amount."

DISCUSSION

Involvement of the heart muscle in hemochromatosis is by no means uncommon. Bork,[1] in his study of the pathology of the disease, states that in practically all his autopsies there was found considerable pigmentation in the muscle fibers of the heart. Sheldon[2] states that the heart muscle is pigmented in at least 90 per cent of the cases, the pigment often being present in huge amounts. Blanton and Healy,[3] in their review of 22 cases, state that a half showed hemochromatosis within the heart muscle, and that the pigment was generally situated intracellularly at the nuclear poles; fibrosis of the heart muscle was found only once, and was not of marked degree. It is evident from these reports that pigmentary deposits in the cardiac muscle are very frequent but that they seldom lead to marked fibrotic changes.

So far as the case under consideration is concerned, it will be noted that there was very extensive pigmentary deposit and that this was associated with extensive fibrosis of the heart muscle. Furthermore, although the patient had suffered from substernal pain during life, the gross and microscopic examination of the heart showed almost normal coronary vessels. It would therefore seem logical to assume that the fibrosis in this case was associated with the pigmentary deposit.

It is necessary however to discuss one other possibility: there is a group of cases of hemochromatosis which have been described, particularly by French authorities, in which cardiac failure, probably of a different origin, is a prominent feature. We refer to the syndrome described by Clerc, Bascourret and Andre,[4] by de Gennes, Delarue and de Véricourt[5] and by Bezançon, de Gennes, Delarue and Oumansky,[6] which is characterized by the association of hemochromatosis with infantilism and cardiac failure. This syndrome is described as pigmentary cirrhosis with infantilism, cardiac insufficiency and multiple endocrine aplasia, or as the "endocrinohepatocardiac" syndrome. The essential features of this syndrome are (1) its occurrence at an age which is definitely below the average of most patients with hemochromatosis; (2) an involvement of the endocrine glands, particularly the testes which are atrophic; (3) the occurrence of infantilism as part of the syndrome; and (4) death from cardiac failure. Judging from the description of the French writers the origin of the cardiac failure in these patients is not in the heart muscle itself, because the pathologic changes in the heart muscle are often not particularly pronounced, but is to be explained on an endocrine basis. De Gennes, Delarue and de Véricourt[5] speak of the condition as a true polyglandular syndrome. They mention the fact already commented on, that although there is evidence of hemochromatosis of the myocardium in most autopsied patients, cardiac insufficiency is rare. They discuss the different types of cardiac failure of endocrine origin, and point out that Walser has described cardiac failure caused by ovarian insufficiency, and that the cardiac insufficiency of thyrotoxicosis and that caused by thyroid insufficiency are well known. They also speak of the role of the adrenals in the production of cardiac insufficiency, the circulatory failure of Addison's disease being a well-known example of this condition. They conclude that in this particular group of cases the cardiac failure is of endocrine origin rather than caused by the pigmentary changes in the heart muscle. As a matter of fact, Bezançon and his co-workers[6] had put forward this same explanation two or three years earlier.

In the case under discussion — a well-developed male of fifty-four — there was no evidence of infantilism, and the autopsy did not indicate any extensive degeneration of the endocrine system except for the pancreas and, to a lesser extent, the thyroid gland. Even in the pancreas fairly normal islands of Langerhans often stood out in the midst

of areas of connective tissue, and while the patient had a high blood sugar, only a trace of sugar was present in the urine and the usual picture of pronounced diabetes was lacking. There was no evidence of testicular atrophy.

CONCLUSIONS

1. The heart muscle is the site of pigmentary infiltration in a large proportion of patients with hemochromatosis.

2. This pigmentary deposit seldom leads to extensive interstitial myocarditis.

3. Occasionally, as in the case reported, interstitial changes occur, and these may be so widespread that they are capable of causing fatal congestive heart failure.

REFERENCES

1. Bork, K.: Zur Lehre von der allgemeinen Hämochromatose. Virchows Arch. f. path. Anat. 269:178-208, 1928.
2. Sheldon, J. H.: Haemochromatosis. Lancet 2:1031-1036, 1934.
3. Blanton, W. B., and Healy, W.: Hemochromatosis; report of four cases. Arch. Int. Med. 27:406-420, 1921.
4. Clerc, A.; Bascourret, M., and André, R.: Cirrhose pigmentaire avec atrophie testiculaire et insuffisance grave du coeur. Bull. et mém. Soc. méd. d. hôp. de Paris 51:1228-1233, 1935.
5. de Gennes, L.; Delarue, and de Véricourt, R.: Sur un nouveau cas de cirrhose pigmentaire avec infantilisme et myocardie. Le syndrome endocrino-hépato-cardiaque. *Ibid.* 1088-1097.
6. Bezançon, F.; de Gennes, L.; Delarue, and Oumansky: Cirrhose pigmentaire avec infantilisme, insuffisance cardiaque et aplasies endocriniennes multiples. *Ibid.* 48:967-974, 1932.
7. de Gennes, L.; Delarue, J., and de Véricourt, R.: Le syndrome endocrino-hépato-cardiaque (étude des cirrhoses pigmentaires avec infantilisme et myocardie). Presse méd. 44:377-381, 1936.

NEWER DRUGS FOR THE TREATMENT OF TAPEWORM INFESTATIONS

Some Results Obtained With Carbon Tetrachloride, Tetrachlorethylene and Hexylresorcinol

J. H. SANDGROUND, D.Sc.*

BOSTON

IN CONSIDERING the essential merits of any anthelmintic, two questions always present themselves: the first concerns its potential toxicity for the host; the second has to do with its efficacy in eliminating the parasite. Other questions also arise, but these are for the most part ancillary.

Among the many medicaments of plant origin which through the centuries have been prescribed for the elimination of tapeworms from man, the drug derived from male fern (*Aspidium* spp.) still enjoys the greatest vogue. The powdered rhizome of the fern, mixed with various other substances, is mentioned by Galen, Pliny and other classical writers. But because treatments often and for unknown reasons fail, efforts to isolate the active principle, filicin, have led to the use, in more recent times, of various extracts of the roots, sometimes in combination with powdered acacia.

As a matter of course, few physicians hesitate to use male fern, for it is the drug most generally recommended in textbooks and treatises on therapeutics. In a recent article, Faust[1] states that "the most reliable drug for all tapeworm infections is probably oleoresin of aspidium." Its potential toxicity, however, must always be kept in mind. The literature is replete with records of severe toxic sequelae, such as headache, vertigo, dyspnea and cyanosis. It often produces gastritis. When absorbed into the system it damages the kidneys and may affect the central nervous system, leading to various optic disturbances, delirium and stupor. An appreciable number of fatalities following the administration of male fern have also been reported. Contraindications do not appear to be well defined, but some of the conditions in which the drug is to be avoided include pregnancy, infancy and old age, anemia, and debility due to chronic disease or acute infection.

Treatment with male fern calls for caution and is always time-consuming. To render it effective the patient's diet should be limited to liquids for at least twenty-four hours, and there should be thorough purgation before treatment is instituted. The drug is intensely bitter, and usually produces nausea and vomiting. In order to control toxicity, therefore, as well as to ensure retention of at least part of the medicine, the dose is often given in two or three gelatin capsules at half-hourly intervals. To avoid emesis several recent writers have strongly recommended administration by transduodenal tube, an elaborate procedure, and a discomforting one for the patient.[2] That male fern is highly efficacious when it has been freshly extracted, assuring high potency, and when the patient, through attention to diet and to preliminary purgation, has been properly prepared for treatment, is not to be gainsaid (Magath and Brown[3]). But it is equally true that the results obtained with this drug are exceedingly erratic, even when the patient is hospitalized to secure optimum conditions for treatment.

Another widely used vegetal principle for tape-

From the Department of Tropical Medicine, Harvard Medical School, Boston.
*Assistant professor of helminthology, Harvard Medical School.

worm treatment is pelletierine, a mixture of alkaloids extracted from the bark of the pomegranate (*Punica granatum*). The relatively insoluble and more stable sulfate of pelletierine with tannin is said to be the least toxic and most efficacious of the several forms in which the drug is available. Nevertheless, it leaves much to be desired. In any of its forms, pelletierine is very disagreeable to take and is liable to produce nausea, vomiting, and in large doses, cerebral symptoms. Again, effectiveness is dependent on preparing of the patient by restricting the diet for a day or two and by rigorous purging before and after treatment.

Pelletierine is usually prescribed after failure with male fern. However, as many of the patients seen by us attest, even Tanret's pelletierine, a highly lauded and expensive proprietary product, often fails to achieve its purpose. The majority of our patients in Boston give a history of from one to several unsuccessful treatments with either male fern or pelletierine or both, and not a few were discouraged at the prospect of getting rid of their insidious guest. An extreme commentary on the unreliability of standard tapeworm remedies is found in the *British Medical Journal,* where a correspondent[4] tells of failing repeatedly to deparasitize a patient, and of finally resorting to operation, at which *the worm was expelled by flushing the intestine with 1 per cent iodine solution!*

A proper evaluation of male fern or pelletierine as taeniacides and as drugs liable to produce serious toxic sequelae or fatalities is impossible for lack of statistics, but they obviously do not approach the standards attained by a number of anthelmintics that have been latterly introduced for the treatment of other helminth infestations. Progress in this branch of therapy has now reached the point where, for several species of worms, a choice of highly effective drugs is available and the ideal method of treatment is actually envisaged. This ideal anthelmintic has been defined in terms of absolute safety for the patient and the complete absence of contraindications to its use. It must be easy to administer and not unpleasant to take. Where large masses of people are in need of treatment, the drug should be cheap and easily obtainable in a pure form, and should possess a high order of efficacy. Safety for the patient is naturally a prime requirement of any drug. Where tapeworm infestations are involved, only rarely can the parasite be charged with such pathogenic potentialities as to warrant taking measures for its expulsion which may jeopardize the patient's life.

As might be expected, the perfect taeniacide is still to be discovered. Starting with an unexpected demonstration of the efficacy of carbon tetrachloride in a case of *Taenia solium* infestation, during the past eight years we have sought to evaluate this and two other drugs that have less objectionable features than the remedies now commonly employed. Despite unremitting efforts, however, we have been able to outline the course of treatment in only 38 cases. Though this series is too small to warrant final conclusions, our results may be of interest and may serve as a guide to the practitioner.

The number of species of tapeworm that normally may affect man is small, and so far as present information indicates, all these species yield to the same drugs in a nonspecific manner. By far the commonest species of tapeworm involved in our cases from the Boston region was *T. saginata,* whose infectious cysticercus stage occurs in beef. *T. solium,* the armed or hooked tapeworm of porcine origin, is veritably nonexistent in this region, and is a rarity in most countries with enlightened systems of meat inspection. Our experience with this species is represented by 3 cases which we treated under primitive field conditions in Yucatan and South Africa. Included in our Boston series also are 5 cases of infestation with *Diphyllobothrium latum,* the broad fish tapeworm which is occasionally encountered among the foreign-born members of the community, especially those coming from regions bordering on the Baltic Sea.

BIOLOGICAL FACTORS IN RELATION TO PROBLEMS OF TREATMENT

From the zoological viewpoint, a tapeworm represents a self-perpetuating colony of organisms (the segments or proglottids) each of which autonomously performs the functions of food assimilation and sexual reproduction. The head (scolex) with its suckers is the organ with which the entire chain or strobila of segments secures a hold on the wall of the small intestine, usually the lower duodenum. Tapeworms increase in length by budding off new segments. The zone of proliferation is in the neck region, immediately behind the scolex. As the terminal segments mature and become gravid, they spontaneously detach themselves and are passed out singly or in short rows. It is by the passage of segments that infections are usually diagnosed, this being done more often by the patient than by the physician or laboratory worker. For several reasons the microscopic search of the feces for eggs is not a reliable index of infestation. When the parasite is subjected to the influence of irritating drugs and other adverse conditions, the longitudinal muscle fibers that hold the segments together may rupture at any point. But unless the scolex is rendered nonviable, regeneration will eventually occur. Consequently the expulsion of the scolex furnishes the only immediate

evidence of a final or complete cure. Yet several hours may elapse after treatment before peristalsis delivers the parasite. In this event it often happens that the chain is broken into numerous segments and fragments, variable in size and appearance. The scolex may well be among these isolated scraps, but to find it involves a tedious as well as odious washing of the feces through sieves. In addition, it requires an ability to recognize the scolex that is not often possessed by the nonspecialist.

Thus, failure to identify the scolex does not necessarily mean that it has not been expelled or that treatment should be repeated. In any event, the patient should be spared a second treatment until some time has elapsed, for the toxic effect of most anthelmintics is cumulative. In cases where the scolex has not been recovered, the passage of sufficient time for regeneration of the strobila becomes the critical test of cure. Therefore, in order to assess the efficacy of the drug it is necessary to keep a check on the patient for a considerable period, during which he must observe every precaution against reinfection.

The potential longevity or natural life span of these parasites is reliably known to be not less than from twenty to thirty-five years. Hence natural death of the parasite and spontaneous cure of the patient are hardly likely to occur within the ordinary period of observation. The essential question is, How long must be the period of absence of signs of infestation before the test treatment can be accounted successful? In the majority of unsuccessful treatments with male fern, segments reappear in the stools within six weeks. Insofar as experimental studies have shown that the species of tapeworms here considered come to maturity and release segments within sixty to seventy-five days after the infectious larval stages have been ingested, from ninety to one hundred days has been regarded as a conservative period of probation by the few investigators who have considered this factor in evaluating results.[5] As our results have shown, this period of freedom from passing segments does not afford a reliable index of the taeniacidal value of all drugs; for we have had several cases treated with hexylresorcinol who claim to have been free from segments for as long as eight months before recidivism became manifest. In these cases the possibility of a renewal of the infestation cannot, of course, be entirely excluded; but it seems highly improbable, for even were larval infestation of beef less rare than it is, our patients have been so worried by their infestations that they have needed no urging in order to adopt the strictest dietary precautions.

CARBON TETRACHLORIDE

Before presenting our own observations, it will will be well to review briefly the history of carbon tetrachloride as an anthelmintic, pointing out some of the virtues of the drug as well as its shortcomings.

Before the inauguration of a formal project for the standardization and development of new anthelmintics by the Bureau of Animal Industry of the United States Department of Agriculture, the attitude toward anthelmintic medication was one of uncritical empiricism. As a result of a series of critical experiments in 1921, Hall[6] discovered that carbon tetrachloride (CCl_4) was an excellent remedy for canine ancylostomiasis, and recommended the trial of the drug as an anthelmintic for man. This suggestion was almost immediately acted upon, but before the drug became widely adopted as a specific against hookworm, exhaustive tests were carried out on many subjects, including criminals who were about to be executed.[7] At first, carbon tetrachloride appeared to be completely lacking in toxicity. Within a few years of its introduction it had been administered to millions of people in tropical and subtropical countries, where, on the score of its general safety and relative cheapness, it has become the drug of choice for the treatment of ancylostomiasis. Used with ordinary discretion it gives admirable results, as indicated by Lambert,[8] who has reported 100,000 treatments for hookworm among the natives of the South Pacific islands, without a single death and with few untoward sequelae. In Egypt, where 5 cc. is the routine dose for adults, Tomb and Helmy[9] have recently reviewed the question of the toxicity of carbon tetrachloride on the basis of the treatment of 1,600,000 patients. Nineteen fatalities were recorded, but the majority of these, it is claimed, could have been prevented. The occurrence of occasional fatalities has led to a comprehensive investigation of the pharmacology of this compound.[10]

Because of its remarkable record of safety in an enormous number of cases, carbon tetrachloride must be recognized as one of the most valuable drugs in the entire pharmacopoeia. Yet any notion that it is innocuous has been dispelled. To some extent it is always absorbed into the system, and damage, particularly to the liver parenchyma, consistently follows, even though the patient may show no clinically recognizable symptoms. To reduce absorption from the intestine, an effective saline purge (preferably sodium sulfate) should be administered either with the anthelmintic or within an hour after taking it. All liquids containing alcohol, and all foods rich in fats, both of which tend to enhance absorption, should be enjoined

for at least a day before and after treatment. It is imperative that there be prompt purgation within a few hours, and in cases of stubborn constipation, enemas or other methods of procuring elimination must be used.

In this connection a note of warning is necessary, the opinion having been expressed that some of the deaths following carbon tetrachloride have been due to too vigorous purgation with saturated magnesium sulfate solution rather than to the poisonous action of the drug. Chronic or acute cirrhosis, whether due to alcoholism or to other causes, and kidney disease are mentioned as the outstanding contraindications to the exhibition of carbon tetrachloride; the drug should be combined with oil of chenopodium in cases where round worms (*Ascaris lumbricoides*) are also harbored. To minimize the effect on the liver, it is advised that the blood-calcium reserve be built up and that carbohydrates in the diet, particularly sugar, be increased for some days before treatment. A certain amount of nausea, dizziness or headache is to be expected, but the patient should not be alarmed, for these symptoms usually disappear as soon as the bowels move.

In some cases, deaths following the administration of carbon tetrachloride have been ascribed to an idiosyncrasy. Furthermore, toxicity does not appear to bear a direct relation to the dosage. On occasion, but apparently unintentionally, as much as 50 cc. — which is almost ten times the usual dose — has been administered without evoking serious symptoms of intoxication.[11] On the other hand, deaths have been recorded following the taking of as little as 1.5 cc. It is well to remember, however, that in extended series of treatments given under field conditions, where physical examination is necessarily omitted, the death rate is probably no higher than 1 per 100,000. Most of our patients were well-nourished adults, but we have never found it necessary to give more than 4 cc. In the case of an aged and rather debilitated woman, 3 cc. was given, and in the case of a boy of twelve caution suggested that only 2 cc. be administered.* The drug, given either in water or with a little milk, has always been well tolerated, although there is usually some dizziness and drowsiness during the first hour. As our results bear witness, for effective treatment against tapeworm it is not at all necessary that the patient be starved before treatment or that there be a preliminary purgation, but on general principles patients have been advised to restrict their supper to toast and milk, and to have an enema on the evening before taking treatment. The drug is given the first thing in the morning, the patient refraining from eating until good purgation has occurred. The tapeworm is usually expelled within two or three hours after treatment, and thereafter the patient may resume normal activity.

*For young children, Lambert[8] prescribes 0.2 cc. for each year of age.

Deriving their opinion by analogy from the results of therapeutic tests with tapeworm-infested dogs, Hall and Shillinger[12] at first declared that carbon tetrachloride was probably of little value against tapeworms in man or in other animals; Chandler and Mukerji,[13] working in India, concurred. It is interesting to observe that these early opinions, based as they must have been upon personal impression rather than upon tests, were completely reversed within a few years.

Attention was first called to the value of carbon tetrachloride as a specific against the tapeworms of man by Daubney and Carman,[14] who while treating hookworm patients in East Africa in 1928 noticed that after the administration of a mixture of carbon tetrachloride and oil of chenopodium tapeworms were often passed. The incidence of *T. saginata* among these raw meat-eating natives is extremely high, and provides ample opportunity for testing taeniacidal drugs. On testing the effect of 4 cc. of carbon tetrachloride on 30 patients, Daubney and Carman found that after a lapse of seven weeks only 1 patient was still passing tapeworm segments, a therapeutic efficiency of 97 per cent. Two interesting and rather significant observations derived from further tests were these: (1) the efficacy of the drug appeared to be reduced rather than enhanced by subjecting the patient to preliminary catharsis; (2) the tapeworm was usually dead on expulsion and had undergone fragmentation, so that the scolex was rarely found attached.

Other investigators have shown that a detached scolex undergoes rapid degeneration, so that it can scarcely be recognized when found in the feces. Continuing studies on the treatment of tapeworm infestations in Kenya Colony, Carman[15] recorded comparably favorable results in from 2500 to 3000 natives who were given a mixture of 4 cc. carbon tetrachloride and 1 cc. oil of chenopodium.* The treatments were given on an outpatient basis at field posts, without a single instance of untoward symptoms. Similarly enthusiastic reports on the efficacy of carbon tetrachloride as a convenient and effective drug for the removal of *T. saginata* have recently appeared in the literature of many countries; for example, Kemp,[16] Hoffman[17] and Talice.[18]

The first 4 patients in the series presented in Table 1 applied for treatment in the field while

*Although it has long been known that oil of chenopodium is by itself often capable of expelling tapeworms, the investigations of Maplestone and Mukerji[19] have shown that the carbon tetrachloride in the mixture here mentioned is the more effective of the two.

we were on expeditions in Yucatan and Rhodesia, where, without facilities for accommodating the patient, it was impractical to continue observation for more than two hours. Within this period, in 2 of these 4 cases we were able to confirm the expulsion of the worms with scolices attached; in the other 2, final assessment of efficacy could not be made. The remaining 12 cases, including 2 cases of *D. latum* infestation, were treated in or near Boston, either in hospitals or in the patient's home under the care of the family physician. In Case 33,

Table 1. *Results of Treatment with Carbon Tetrachloride.*

CASE NO.	SPECIES	DOSE	RESULTS OF FOLLOW-UP
		cc.	
1	*T. solium*	4	Worm passed up to neck. No follow-up.
2	*T. solium* and *T. saginata*	4	Three worms passed, two with scolex.
3	*T. saginata*	4	Worm passed with scolex.
4	*T. saginata*	3	Worm passed in fragments. No follow-up.
5	*D. latum*	4	Scolex passed.
6	*T. saginata*	4	Worm passed up to neck. No later report from patient.
7	*T. saginata*	4	Worm passed in fragments. Patient free from segments after 28 months.
11	*T. saginata*	4	Two worms passed with scolex.
16	*T. saginata*	4	Treatment at home. Patient free from segments after 18 months.
27	*T. saginata*	4	Worm passed with scolex.
28	*D. latum*	4	Worm in fragments (with scolex?). Patient free from segments after 10 months.
30	*T. saginata*	4	Worm passed with scolex.
33	*T. saginata*	4	Drug vomited on two occasions. No cure.
34	*T. saginata*	2	Worm passed with scolex.
36	*T. saginata*	4	Worm passed with scolex.
38	*T. saginata*	4	Worm passed in fragments. Patient free from segments after 10 months.

the hospital intern reported that the patient could not tolerate the drug and vomited each time it was given. Although several feet of the worm chain were passed, this case is reckoned as a failure, but it might justifiably have been excluded from the series. Of the remaining 11 cases, reports subsequent to treatment were secured in all but 1 (Case 6), and although search for the scolex was futile in several cases, the statements of the patients indicated that treatment was completely satisfactory. These results are very much in keeping with the favorable reports to which reference has already been made.

TETRACHLORETHYLENE

Like carbon tetrachloride, tetrachlorethylene (C_2Cl_4) was also introduced into medicine via the veterinary field. Before its trial in human beings was suggested, Hall and Shillinger[20] had found the drug to be almost as efficacious against hookworm in the dog as was carbon tetrachloride, over which it appeared to have two advantages: it had a less unpleasant taste; and, being less soluble in water, it was less readily absorbed through the intestine, so that it produced no detectable pathologic or functional damage to the liver, even when administered together with alcohol to increase absorption in test animals. Tetrachlorethylene has been given in innumerable cases (probably several hundred thousand) of hookworm infestation without any fatalities, or cases, of serious intoxication being reported. In the literature it is mentioned that occasionally there is vomiting, and slight vertigo of an anesthetic rather than a toxic nature. Although tetrachlorethylene lacks the toxicity of carbon tetrachloride, it is not used on such a massive scale as the latter. This is possibly because of its slightly greater cost, and possibly because of a general conviction that in actual practice the dangers of carbon tetrachloride are negligible.

Because of the reputed superiority from the pharmacologic standpoint of tetrachlorethylene over carbon tetrachloride, we attempted to determine its taeniacidal value. The experience of Hall and Shillinger[20] indicated that the drug was of no value against tapeworm in dogs, but it does not appear to have been adequately tested for these infestations in man. In the literature, the only reference that we have found is the brief and incidental mention of Maplestone and Mukerji[19] that they tried tetrachlorethylene (dosage not stated) on three patients with no apparent effect on the tapeworm.

Unfortunately, the number of cases in our series is too small to warrant final conclusions as to the value of tetrachlorethylene against *T. saginata*. Altogether it was tried in 8 cases, the dosage being generally 4 cc. and the method of treatment being similar to that with carbon tetrachloride. On each occasion a large portion of the strobila extending up to the attenuated neck region was expelled, but the scolex was never found attached. In 3 cases we received no report from the patient after his discharge from the hospital. In 1 case, segments reappeared twelve days after treatment, while in another they did not reappear until nearly three months had elapsed. The fifth case concerned a patient who was admitted to the hospital with severe jaundice and fever of undiagnosed origin. The only positive laboratory finding was a tapeworm infestation, which the physician considered might have involved the bile duct and caused obstruction. In view of the patient's condition tetrachlorethylene appeared to be the drug of choice, and 3 cc. was administered instead of the usual 4 cc. A mass of tapeworm segments was passed in due course, but the scolex was not found. After an exploratory operation a month later, the patient died. At autopsy a large liver abscess, possibly amebic, was found, but the pathologist reported no trace of a tapeworm in the intestine. The conditions presented in this case may be regarded as an ideal set-up for the crucial test of a drug's efficacy. In the 2 remaining cases of this series, according to reports received about six months after

treatment, there was no recurrence of infestation. There consequently appear to have been cures in 3 of the 8 cases treated with tetrachlorethylene.

HEXYLRESORCINOL

Hexylresorcinol was introduced by Leonard[21] in 1924 for the treatment of genito-urinary infections. In preliminary tests, it was taken by Leonard and several volunteers in 1-gm. doses, four times a day for two consecutive weeks, without any toxic manifestations. In 1930, Lamson, Ward and Brown[22] first drew attention to hexylresorcinol as an anthelmintic that was especially effective against *A. lumbricoides* and other nematode parasites in the intestine, and that indeed closely approached the ideal anthelmintic. The drug has been very widely used as a urinary antiseptic, and has been given as an anthelmintic to thousands of persons without serious sequelae.

Hexylresorcinol is soluble in alcohol, glycerin, and vegetable oils, but only slightly in water. Because of its affinity for proteins, solutions in olive oil, for example Caprocol, are likely to be inert. For this reason hexylresorcinol is best given as an anthelmintic in the form of sugar-coated pills, on an empty stomach. Lamson et al.[22] prescribed doses ranging from 0.15 gm. for young children to 1.0 gm. for adults.

Our tests of hexylresorcinol as a taeniacide were initiated early in 1931. In the following year, Lamson and Ward[23] mentioned having rid dogs of tapeworms with this substance and having tried it in several patients who expelled yards of worms without the scolex. More recently, Maplestone and Mukerji[24] in Calcutta reported treating 10 cases of *T. saginata* with 1 gm. doses of this drug in hard-gelatin capsules. Reports from 9 of the 10 patients three months after treatment showed the return of segments in the stools of 4. The authors discontinued their trials of hexylresorcinol on the ground that carbon tetrachloride was cheaper and yielded better results.

In our series of 24 cases, initial tests with hexylresorcinol were made with 1 gm. doses of sugar-coated pills.† The following simple procedure was usually adopted. After a light evening meal the intestinal tract was cleared as much as possible without incommoding the patient. The pills were administered on arising next morning, with an unlimited amount of water to reduce or prevent the slight burning sensation in the epigastric region that is sometimes the subject of complaint.* A few of our female patients vomited, — largely, it appears, because of the revival of unpleasant memories associated with previous experiences with male fern, — but the distress appears never to have been severe. A mineral oil or saline purge was given about an hour after the drug, and food was withheld for another few hours. Often the parasite was expelled much shriveled and evidently dead. However, since fragments of the chain may continue to pass for at least forty-eight hours, we usually dispense with a search for the scolex in the feces. When some of the patients reported remission of segments, we decided to give subsequent treatments with larger doses to all except debilitated subjects. The safety of much larger doses had already been indicated by Leonard's[21] experiments, and we ourselves did not observe any untoward effect after administering three 1-gm. doses of hexylresorcinol at approximately hourly intervals on two consecutive mornings.

Table 2. *Results of Treatment with Hexylresorcinol.*

CASE NO.	SPECIES	DOSE	RESULTS OF FOLLOW-UP
		gm.	
9	*T. saginata*	1.0	Free from segments after 14 mo.
10	*T. saginata*	1.0	Free from segments after 13 mo.
11	*T. saginata*	1.0	Reappearance of segments after 4 mo.
		3.0*	Reappearance of segments after 3 mo.
12	*T. saginata*	1.0	Free from segments after 11 mo.
13	*D. latum*	1.0	Free from segments after 8 mo.
14	*D. latum*	0.8	Reappearance of segments after 4 mo.
		2.0*	Free from segments after 14 mo.
15	*T. saginata*	1.0	Reappearance of segments after ½ mo.
16	*T. saginata*	1.0	Reappearance of segments after 3 mo.
		3.0*	Reappearance of segments after 7½ mo.
18	*T. saginata*	2.0	Reappearance of segments after 5 mo.
19	*D. latum*	3.0	Examination after 1 mo. negative. No further report.
20	*T. saginata*	1.2	No report from patient.
21	*T. saginata*	3.0	No report from patient.
22	*T. saginata*	3.0	Scolex passed (?). Freedom from segments after 5 mo.
23	*T. saginata*	2.6	Reappearance of segments after 4 mo.
		2.6*	Reappearance of segments after 2½ mo.
24	*T. saginata*	1.2	Reappearance of segments after 4½ mo.
30	*T. saginata*	3.0	Reappearance of segments after 1 mo.
31	*D. latum*	4.4†	Free from segments after 43 mo.
32	*T. saginata*	6.0†	Free from segments after 12 mo.
33	*T. saginata*	2.0	Reappearance of segments after 2½ mo.
34	*T. saginata*	1.2	Reappearance of segments after 3½ mo.
36	*T. saginata*	3.0	Reappearance of segments after 2 mo.
37	*T. saginata*	2.4	Free from segments after 5 mo.
38	*T. saginata*	3.0	Reappearance of segments after 2 mo.
35	*T. saginata*	3.0	No report from patient.

*Second treatment.
†Given in two equal doses on successive days.

As shown in Table 2, hexylresorcinol is to be credited with success in at least 7 out of 24 trials. The medication may be effective in doses as low as 1 gm. On the other hand, a dose of 3 gm. given at hourly intervals may fail. Whether or not the method of administration is the factor responsible for the lack of consistency in the results is a question requiring further investigation.

The observation that after exposure to an anthelmintic a tapeworm may not evince signs of its con-

†Supplied through the courtesy of the manufacturers, Sharp and Dohme, Philadelphia.

*Hexylresorcinol has the qualities of a local irritant, producing a burning sensation with superficial necrosis on the tongue and on the gastric mucosa. Hence children are cautioned against chewing the sugar-coated pills. The irritant effects are usually mild and transient; the damage to the mucosa is rapidly repaired and is clinically negligible.

tinued vitality by regenerating its lost segments within as long a period as seven months is an entirely novel one. Because of this, it is difficult to arrive at a true assessment of the drug's taeniacidal potentialities unless the co-operation of the patient in the scrutiny of the stools for more than six months is secured. In our experience, this co-operation has often been difficult to obtain. It is obvious that had we adopted the usual criterion of cure — freedom of segments for three months — at least 9 more successes would have been added in this series, giving hexylresorcinol an efficiency score at least comparable to that of male fern. From the circumstances in those cases showing delayed relapse, we believe that the possibility of reinfestation can be discounted. A more plausible explanation, in our opinion, is that the effect of the drug may fall just short of being lethal, and that the worm may display an unusually slow recovery from this injury.

SUMMARY

Following an incidental observation in 1929 on the efficacy of carbon tetrachloride in causing the expulsion of *T. solium* and *T. saginata,* 38 patients infested with either *T. saginata* or *D. latum* have been subjected to tests on the taeniacidal value of three relatively innocuous anthelmintics: carbon tetrachloride, tetrachlorethylene, and hexylresorcinol. Most of these patients were treated in hospitals or in their own homes in or near Boston, and nearly all presented histories of previous unsuccessful treatments on one or more occasions with either male fern or pelletierine or both.

In 12 of 16 cases treated with carbon tetrachloride — the usual dose being 4 cc., — the parasite was effectively eliminated. The results in 3 cases could not be properly followed up. In 1 case the patient was unable to retain the drug. These results are in accord with recently expressed opinions that carbon tetrachloride is the most effective remedy for the treatment of tapeworm infestations in man. Ordinarily, treatment with this drug is quite safe and contraindications are few and well defined. It is superior to the classical male fern not only in efficiency but also in being less inconvenient, less time-consuming and less expensive.

Tetrachlorethylene has a lower toxicity than carbon tetrachloride, but in a test series of 8 cases it was effective in only 3.

Hexylresorcinol, given in sugar-coated pills, in quantities ranging from 1 to 6 gm. (in divided doses), has been used effectively in 7 of 24 cases. The main portion of the tapeworm strobila is always expelled, but the scolex may remain viable even though the passage of segments in the feces may not be resumed until several months have elapsed.

Carbon tetrachloride may be confidently recommended on the score of its efficacy and general safety. Tetrachlorethylene and hexylresorcinol are reputed to be less toxic; because of their safety, either of these drugs may be prescribed for patients in a debilitated condition where other remedies are contraindicated. Further trials with larger or repeated doses, after preliminary evacuation of the gastrointestinal tract, may show that hexylresorcinol and tetrachlorethylene have a greater taeniacidal value than is indicated by the present experience.

I am indebted to Dr. George C. Shattuck for arranging facilities for treatments in various local hospitals and for his encouraging interest in the work.

REFERENCES

1. Faust, E. C.: The Pharmacopeia and the physician; the use of anthelmintics. J. A. M. A. **108**:386-392, 1937.
2. Golob, M.: Transduodenal treatment of Taenia saginata infestation. J. Lab. & Clin. Med. **20**:841-843, 1935.
3. Magath, T. B., and Brown, P. W.: Standardized method of treating tapeworm infestations in man to recover the head. J. A. M. A. **88**:1548-1549, 1927.
4. Clements, R. G.: Treatment of tapeworm. Brit. M. J. **2**:326, 1935.
5. Penfold, W. J., and Penfold, H. B.: Taenia saginata: its growth and propagation. J. Helminthology **15**:41-48, 1937.
6. Hall, M. C.: The use of carbon tetrachlorid for the removal of hookworms. J. A. M. A. **77**:1641-1643, 1921.
7. Leach, C. N.; Haughwout, F. G., and Ash, J. E.: The treatment of hookworm infestation with carbon tetrachloride: a clinical and laboratory study. Philippine J. Sc. **23**:455-512, 1923.
8. Lambert, S. M.: Hookworm disease in the South Pacific; ten years of tetrachlorides. J. A. M. A. **100**:247-248, 1933.
9. Tomb, J. W., and Helmy, M. M.: The toxicity of carbon tetrachloride and its allied halogen compounds. J. Trop. Med. **36**:265, 1933.
10. Lamson, P. D.; Minot, A. S., and Robbins, B. H.: The prevention and treatment of carbon tetrachloride intoxication. J. A. M. A. **90**:345-349, 1928.
11. Smillie, W. G., and Pessoa, S. B.: Treatment of hookworm disease with carbon tetrachloride. Am. J. Hygiene **3**:35-45, 1923.
12. Hall, M. C., and Shillinger, J. E.: Miscellaneous tests of carbon tetrachloride as anthelmintic. J. Agr. Research **23**:163-192, 1923.
13. Chandler, A. C., and Mukerji, A. K.: Carbon tetrachloride as an anthelmintic. Indian M. Gaz. **60**:61-69, 1925.
14. Daubney, R., and Carman, J. A.: Helminthic infestations of natives in the Kenya Highlands. Parasitology **20**:185-206, 1928.
15. Carman, J. A.: A note on the clinical aspect of the treatment of taeniasis with carbon tetrachloride. Tr. Roy. Soc. Trop. Med. & Hyg. **25**:187-190, 1931.
16. Kemp, A. H.: Intestinal parasites: a suggestion in the method of treatment. J. A. M. A. **96**:1948-1949, 1931.
17. Hoffman, W. A.: Intestinal parasiticides. Porto Rico J. Pub. Health & Trop. Med. **7**:51-61, 1931.
18. Talice, R. V.: El tetraclururo de carbono come anthelmintica para las tenias del Hombre. 8e Reunion d. l. Soc. Argentina Pat. reg. del Norte, Buenos Aires, pp. 550-553, 1936.
19. Maplestone, P. A., and Mukerji, A. K.: Carbon tetrachloride in the treatment of taenia infections. Indian M. Gaz. **66**:667-670, 1931.
20. Hall, M. C., and Shillinger, J. E.: Tetrachlorethylene, a new anthelmintic. Am. J. Trop. Med. **5**:229-237, 1925.
21. Leonard, V.: Secretion of bactericidal urine and disinfection of the urinary tract following oral administration of certain alkyl derivatives of resorcinol. J. A. M. A. **83**:2005-2012, 1924.
22. Lamson, P. D.; Ward, C. B., and Brown, H. W.: An effective ascaricide — hexylresorcinol. Proc. Soc. Exper. Biol. & Med. **27**:1017-1020, 1930.
23. Lamson, P. D., and Ward, C. B.: The chemotherapy of helminth infestations. J. Parasitol. **18**:173-199, 1932.
24. Maplestone, P. A., and Mukerji, A. K.: Hexylresorcinol as an anthelmintic. Indian M. Gaz. **67**:610-612, 1932.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTEMORTEM AND POSTMORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT, M.D.

TRACY B. MALLORY, M.D., *Editor*

CASE 24071

PRESENTATION OF CASE

First Admission. A thirty-three-year-old, white, Canadian housewife entered the hospital with the complaint of abdominal pain of eight days' duration.

Eight days before entry she noticed the onset of mild, crampy, low back pain, which during the day became gradually more severe and radiated to both lower quadrants, particularly the right. The patient said the pains resembled labor pains. She had complete anorexia with frequent nausea and would have gone to bed if she had not had to take care of four small children. She also became somewhat constipated, and during the two days before entry her bowels did not move. On the second day of her illness the pain became localized in the right lower quadrant, but two days later it became much more severe and generalized, persisting thus up to the time of entry. She had severe nausea and vomited once on the morning of entry. She had had no previous attacks, but for several months she had been subject to "bilious spells" with headache, nausea and vomiting which lasted one or two days and occurred about every two weeks. For some months she had felt tired and physically below par. She had had no fever or other symptoms except one brief shaking chill on the morning of entry.

Her menstrual periods had always been regular up to one year before entry, when they became prolonged, lasting ten or twelve days, with excessive bleeding and clots. Two months before entry the interval between periods became suddenly shortened to eighteen days, and the menorrhagia persisted. Her last period ended nine days before entry, but two days later she flowed again for a single day.

She was born in Nova Scotia and for the four years before entry had lived in a town near Boston. She had never been anywhere outside of the northeastern part of North America. However, her husband, in the course of his business, periodically received shipments of snails from South Africa which both she and he handled and sorted for distribution to museums and other institutions in this country. Her past history and family history were noncontributory.

Physical examination revealed a well-developed and nourished, pale, listless female, appearing acutely ill. The heart and lungs were negative, and the blood pressure was 126 systolic, 80 diastolic. There was moderate distention of the lower part of the abdomen, and peristalsis was much diminished. The entire abdomen was tender throughout, with exquisite tenderness and spasm in the right lower quadrant. A very tender grapefruit-sized mass could be palpated in that area, and there was marked rebound tenderness. On pelvic examination a large tender mass could be palpated in the right vault, and the left vault was diffusely tender.

The temperature was 103.6°F. by rectum, the pulse 132. The respirations were 24.

The urine examination was negative. The blood showed a red-cell count of 4,000,000 with 60 per cent hemoglobin, and a white-cell count of 26,500. The corrected sedimentation rate of the red cells was 0.1 mm. per minute. The nonprotein nitrogen of the blood serum was 19 mg. per cent, the protein 4.9 gm. per cent, and the chlorides equivalent to 99 cc. of N/10 sodium chloride. On the fourth day an operation was performed. An oblique incision was made over the tender mass centered at the right border of the rectus muscle. When the peritoneum was incised, matted coils of intestine presented. The fibrinous adhesions were easily separated, and a large well-walled-off abscess was found, which apparently lay medial to the cecum. It was aspirated, and drainage wicks were placed into it before closing the wound.

Bacteriological examination of the fluid failed to show any organisms. Two days after the operation her temperature had fallen to normal, and her white-cell count gradually fell to 7700. Over a period of three weeks the wound continued to drain pus which slowly lessened in amount. A culture of the pus on the eleventh postoperative day showed *Staphylococcus aureus*. She was discharged on the twenty-eighth day, at which time no masses could be made out in the abdomen. However, pelvic examination showed definite thickening and induration in the right vault.

Final Admission (five weeks later). After discharge she went to a convalescent home where she stayed up to the time of re-entry. The wound continued to drain moderate amounts of semifluid, green, non-odorous material without any blood or feces. She had a slight dull ache in the region of the sinus, but no severe pain. Her appetite was good and she gained 13 lb. in weight. Her bowel movements were normal.

Physical examination showed the right lower-quadrant scar with a draining sinus. There was some tenderness and spasm in the surrounding area, and pelvic examination showed induration and tenderness in the right vault.

The temperature was 99.2° F., the pulse 85. The respirations were 17.

The urine examination was negative, and the blood showed a white-cell count of 10,500.

On the third day a laparotomy was performed.

Notes on the History

Dr. Somers H. Sturgis: The fact that this patient could still manage to take care of four children gives a pretty good clue that this attack probably was not prostrating or severe. If we can assume that the past history has something to do with the present entry, it is a chronic condition and did not have an acute onset. It would seem that it must be associated with some intestinal trouble. There is nothing to suggest any general systemic disease. She had no fever or other symptoms until the time of entry. She could not have been very sick during the first eight days.

I do not believe that menorrhagia at regular intervals has any particular endocrine significance. It suggests some mechanical involvement of the ovaries or tubes. Clots are not significant. There was gradually increasing shortening of the intervals between periods, with excessive bleeding, but no skipping or lateness of periods.

"Her husband, in the course of his business, periodically received shipments of snails from South Africa which both she and he handled." That seems to be the only association with tropical disease or suggestion of parasitic infestation in the whole history.

In spite of the fact that she had been having trouble for several months she was still well developed and nourished. "There was moderate distention of the lower part of the abdomen, and peristalsis was much diminished." That again suggests lower abdominal trouble. So far as we have gone we can limit ourselves to considering lesions of the intestine or pelvis.

"The corrected sedimentation rate of the red cells was 0.1 mm. per minute." I believe with the new method that is approximately normal. It would seem that she received very adequate drainage, for the temperature fell to normal in two days. It makes us feel that the acute condition was due to the abscess, and draining of that relieved her for the time being.

"A culture of the pus on the eleventh postoperative day showed *Staphylococcus aureus*." I assume that that was a contaminant and need not confuse the picture. As I said before, the process seems to be abdominal. I do not believe we need to consider whether it was a metastatic abscess from other systemic disease. All the difficulty seems to be localized in the abdomen, and therefore the culture is of little, if any, significance.

Differential Diagnosis

Essentially this is the story of a thirty-three-year-old American woman who had had for several months some sort of recurrent, persistent but mild intestinal disturbance which culminated in an eight-day illness, apparently of an inflammatory nature, which started mildly, became severe and terminated in drainage of a large abscess cavity in the abdomen. She had no septic, picket-fence temperature so far as we know during these eight days and was not bedridden. Following this drainage it is important to note that the sinus tract did not close in the five weeks up to her second entry; and also that it did not discharge feces. The first thing we notice in reading over the first paragraph, which concerns the character of the pain in the lower abdomen, is that two days after it started it localized in the right lower quadrant, and that two days later it became generalized and much more severe. That was four days before entry to the hospital.

Could this be an appendix abscess? I do not believe so. If the pain became localized in the right lower quadrant and then two days later spread to the whole abdomen with general tenderness, we would have to assume that the appendix perforated at that time. It seems impossible that she could have had generalized peritonitis from a perforated appendix and could have taken care of the children without any more trouble than she had. It may have been a gangrenous appendix, or an appendiceal abscess may have formed. The fact that the abscess was medial to the cecum would favor the latter. But any process that gives generalized tenderness and pain in the left vault or spreading or generalized peritonitis puts the patient to bed and probably does not form a localized abscess. It does not seem that both the abscess and generalized pain could be explained on the basis of a ruptured appendix alone, and the same thing is true of any other perforation of the bowel, such as that of a diverticulum of the sigmoid, which could cause abscess in that region. If there were abscess formation from perforation of an inflamed diverticulum in the sigmoid, one would expect that the draining sinus would heal within five weeks after operation. Certainly, if the sinus tract resulted from an abscess secondary to perforation of some part of the bowel and did not heal in five weeks, one would expect a fecal fistula. I believe it is of considerable significance that there were no feces in the sinus tract after five weeks. Of course Meckel's diverticulum can give all the symptoms of appendicitis. It can also

give pain in the left side as well as the right; but there again, if a Meckel's diverticulum were inflamed and formed an abscess, one would expect to find *Bacillus coli* in the original drainage of the abscess and, again, that the sinus tract would heal or form a fecal fistula. It is possible that perforation of the intestine into the mesenteric border by foreign body, such as a porcupine quill or needle, might have caused a sterile abscess in the mesentery which could give such a picture as this, and if the foreign body did not come out in five weeks, I suppose it is possible that it might keep the tract open. But there is no history suggesting such a possibility, and we have to let it go at that.

When she came in she had this grapefruit-sized mass in the right vault and tenderness in the left vault, and she might have had salpingitis. If she had gonorrheal salpingitis one would expect symptoms of dysuria, frequency and vaginal discharge when the disease was contracted. These are completely lacking, but in a female they might have been mild and overlooked. One would not expect gonococci on culture at the time of drainage. She might have had a hydrosalpinx which, four or five weeks after contracting the disease, would have been sterile on culture. Again, I should expect the sinus to heal unless there was a secondary infection or a tuberculous salpingitis. Although this thing had been going on for some months she was well-developed and nourished, not emaciated. With a tuberculous pelvic infection that goes on to secondary abscess formation, one would expect examination of the pelvis to show induration. It does not seem to be the picture of tuberculous salpingitis. However, this would explain the chronicity of the sinus tract.

Possibly she had a twisted ovarian cyst or even a pedunculated fibroid that was twisted. Either of these might have become gangrenous. In considering the possibility of perforation of the intestine, I should have mentioned that one would expect sudden prostration. In the same way, in a twisted pedunculated fibroid becoming gangrenous one would expect a sudden prostrating form of trouble. It was eight days, however, after symptoms started before she came to the hospital. Again, it says that the mass was a walled-off abscess, and it seems unlikely that the surgeon would not have seen that it was something queer or suggestive of gangrenous cyst or abscess from gangrene.

I think that the menstrual irregularity that she had does not necessarily mean that the primary trouble was in the ovaries or tubes. Any sort of inflammatory reaction in the lower abdomen or pelvis — and we know she had it — could easily involve the ovary and tube with adhesions, and so forth, sufficient to give her irregularity. I do not believe that it is significant enough to point to the trouble as arising primarily in the pelvis.

How about syphilis? It might have been a broken-down gumma of the mesenteric nodes, but that is all I can say. There is no report of a Hinton test, and no history of contact. I think it is unlikely.

We must next consider unusual infections or infestations. This patient had been living in America; this rules out many of the tropical diseases. *Entameba histolytica* infection is unlikely, because that also comes in the category of perforation of the intestine. Actinomycosis might be the reason for keeping the sinus tract chronic. Actinomycosis of the intestines is not unknown without any other lesions. There is no history, however, of contamination from contact with straw and hay. We have to assume that granules might have been looked for in the smear which was said to be negative, but this does not necessarily rule out actinomycosis. The thing that does rule it out is that she was not emaciated and on the second entry had gained 13 lb. Furthermore, drainage of an actinomycotic abscess would not be adequate treatment; the disease would spread, with more sinus tracts and fistulas five weeks later. I believe she was not sick enough to have had it.

Then comes the question of the snails. Snails do serve as hosts for several parasitic organisms. Would it be fair to ask for a differential count?

Dr. Tracy B. Mallory: On two smears the polymorphonuclears were 63 and 82 per cent respectively. No eosinophils were seen on either occasion. The lymphocytes were 16 and 12 per cent and the monocytes 4 and 16, respectively.

Dr. Sturgis: I am sorry about that because I should like to have found a high eosinophilia. Apparently none were seen. In considering parasites in South Africa, the flukes or flat worms, schistosoma, are prevalent. I believe that there are no cases reported in America that cannot be traced to direct or indirect contact with the parts of the world where the parasite is prevalent. The schistosoma parasite has an encysted state in snails, and human beings can be infected through the skin as well as by the oral route. The parasites may lodge in the pelvic veins where they develop to the adult stage. They have a tendency to locate in the rectum, ovary, bladder and sometimes in the appendix. It seems that a perfectly good case could be worked out for infestation with *Schistosomum hematobium*, the blood fluke, coming in snails in the encysted form, working through the skin, and lodging in the appendix, to give an appendiceal abscess. At the same time I suppose if that were the case she might have a generalized schistosomiasis in the pelvic veins and

pelvic peritoneum, which would explain the things that puzzled me before — the large abscess medial to the cecum and her generalized abdominal tenderness and spasm. The discharge of eggs through the sinus would also explain its chronicity. Perhaps the snail was put in to make it harder, but I will stand by my diagnosis.

Preoperative Diagnosis

Residual appendiceal abscess.

Dr. Sturgis's Diagnoses

Schistosoma infection of appendix with abscess formation.

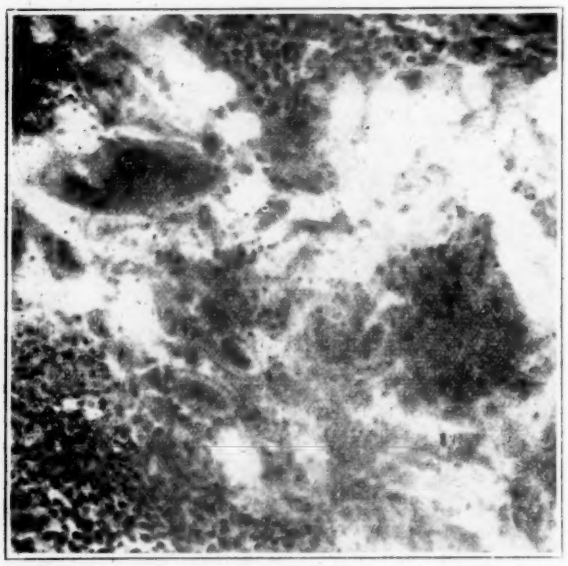
Generalized schistosomiasis of pelvic peritoneum.

Anatomical Diagnosis

Oxyuris infection of the salpinx and pelvic peritoneum.

Pathological Discussion

Dr. Mallory: We have been made very conscious of schistosoma by the recent visit of two South Africans here, and that question came up very definitely in this case after we had examined the tube and found in its walls a lot of peculiar looking ova. However, when we sent the material to some of the experts in the Department of Comparative Pathology at the Harvard Medical School they failed to confirm our suspicions. The accompanying photomicrograph shows a typical



microscopic field. In the upper left-hand corner is a huge giant cell. Below its right-hand end are four or five lozenge-shaped masses with dark central areas and clear hyaline capsules around them. Five or six of these ova are twice as big as the others. True schistosoma have spines, which are easily made out. Whether they are at the end or on the side distinguishes the different species. When the ova in this case were compared with schistosoma it was evident that they were too small, and, moreover, we were unable to find any spines, which are so characteristic of schistosoma. However, sometimes in a section it is difficult to make out the spine because the ova may have been cut at the wrong angle. The ova which most closely correspond in appearance to these are those of the ordinary pinworm, *Oxyuris vermicularis*. With a little research on the part of the laboratory staff we have found a number of papers* reporting about 20 cases of pinworm infestation of the tubes or the peritoneal cavity. Peritoneal infestation has never been reported in males. In many of these cases it has been possible to find the pinworms in the vagina, uterus or tubes, evidently on the way up the genital tract. So I think there is no question that in this case the worms must have climbed up through the vagina and uterus. Whether the inflammatory reaction that develops in these cases is due entirely to the pinworm or whether there is a secondary bacterial inflammation has never been determined with certainty. In most of the reported cases no cultures have been taken. We have in this case the original culture of the abscess, which was sterile, so that we have some evidence against a synchronous bacterial infection.

The gross appearances at operation were very interesting; I am going to ask Dr. Faxon to tell about them.

Dr. Henry H. Faxon: We did not give the same imaginative thought to the problem that Dr. Sturgis has, and with a tender right-lower-quadrant mass we were satisfied that it was an appendix abscess and it was drained. I should like to congratulate him on sorting out the salient features of the history — the mention of snails from South Africa, the bacteriology and the persistent sinus. We were surprised that with an abscess of appendiceal origin there was not more odor to the pus, and with a little more imagination we should have more properly evaluated the findings, but even at the time of discharge we felt that we had been dealing with an appendiceal abscess.

The reason for re-entry was to have an appendectomy performed in accord with our policy that if drainage of an appendiceal abscess has been performed without removal of the appendix, then appendectomy should be carried out two or three months after the first operation to prevent the more than likely chance of future attacks. At

*Chiari, H.: Über das Vorkommen von Oxyuren im menschlichen Eileiter. Virchows Arch. f. path. Anat. 269:730-738, 1928.
Goodale, R. H., and Krischner, H.: Oxyuris vermicularis in the peritoneum. Arch. Path. 9:631-634, 1930.
Jones, W. J., and Bunting, C. H.: Invasion of the fallopian tube by Oxyuris vermicularis. Arch. Path. 11:229-235, 1931.

the time of the first operation no effort was made to find the appendix. At the second operation we explored the peritoneal cavity, still laboring under the mistaken idea that we had drained an appendiceal abscess. When she came in the second time, as Dr. Sturgis logically pointed out, the sinus should have discharged fecal material or it should have closed had the original trouble been caused by her appendix. I made a paramedian incision and under the McBurney incision found the sinus tract matted with coils of intestine. These I freed and found that the sinus tract continued down to a point over the great vessels in the pelvis. There the sinus tract apparently entered into a lymph node in that region. There was a mass involving the right tube and ovary. The left tube was not strikingly abnormal save for small nodules along it. Similar nodules were more easily seen on the right side, where the mass was present. The uterus was tied down, chiefly posteriorly, by adhesions that could be separated fairly readily and seemed of long-standing rather than of short duration. When I saw the appearance of the pelvis the impression I gathered was that it was probably pelvic inflammatory disease. We asked one of the pathologists to come over, and I excised one of the small nodules that appeared on the tube and gave it to him to section. It was about 0.75 cm. in diameter, and on section it was seen to have a well-formed wall with a caseous center. He was completely satisfied that it represented tuberculosis. At the end of the first operation the diagnosis was acute appendiceal abscess; at the second operation the diagnosis was tuberculous salpingitis; after about a week of making myself a nuisance to Dr. Mallory we got as far as schistosoma salpingitis, and after a much longer period than Dr. Sturgis took, we arrived at the correct diagnosis.

Dr. Mallory: This gross appearance of the tubes is apparently very characteristic of the condition which has been reported several times in the American and German literature as pseudotuberculosis, apparently due to pinworms.

Dr. Joe V. Meigs: You find pinworms in appendices. Do they ever perforate?

Dr. Mallory: A significant percentage, perhaps 1 or 2 per cent, of appendices contain pinworms, perhaps more than that in children. In all the literature on the subject there are only one or two papers suggesting that they penetrate its wall, and those are under a cloud of doubt. On the other hand this invasion of the peritoneal cavity via the female genital tract is perfectly well established.

Dr. Faxon: I might say that the appendix was retrocecal and nowhere near the mass in the pelvis. It was perfectly free and grossly normal; on section no lesion was found.

Dr. Francis T. Hunter: In the literature is eosinophilia mentioned?

Dr. Mallory: It usually is found in the local reaction around the ova, but not mentioned in the blood.

A Physician: Did you find the worms?

Dr. Mallory: We made the correct diagnosis long after the patient had gone home. She was not examined for pinworms.

A Physician: Were any whole worms found in the specimen?

Dr. Mallory: No, just the ova; the worms had been destroyed by inflammatory reaction whereas the ova were more resistant and remained behind to produce a foreign-body reaction that closely resembled tuberculosis.

CASE 24072

Presentation of Case

A forty-eight-year-old, white, American housewife entered the hospital with the complaint of severe abdominal pain of thirty-six hours' duration.

She was well and healthy until about six weeks before entry, when she had "intestinal grippe" of three or four days' duration. Epigastric pain was the only symptom she remembered at that time. Thirty-six hours before entry, she was suddenly awakened in the morning by a sharp, griping, midepigastric pain which made her cry out. She got out of bed, defecated a small amount, and vomited some normal-appearing gastric contents. Her physician was called and gave her a hypodermic injection which eased but did not abolish the pain. During the course of the day and evening the pain shifted to the lower abdomen and became cramplike in character. She was given another hypodermic and took "small white pills" every hour. The following morning the pain was somewhat less severe and still localized in the lower part of the abdomen. She had no further vomiting but felt quite nauseated, had anorexia, and raised considerable amounts of gas. Since the defecation at the time of the onset of the pain, she had passed neither gas nor feces by rectum. About eight hours before entry she was given an enema with little result. She had had no cardiorespiratory or genitourinary symptoms, and her menstrual history was negative. Her past history and family history were noncontributory.

Physical examination revealed a well-developed but somewhat emaciated woman sitting upright in bed, breathing rapidly, in obvious discomfort. The skin was dry and flushed, and the tongue

was rough and coated. The heart and lungs were negative, and the blood pressure was 126 systolic, 72 diastolic. The abdomen showed boardlike spasm and was moderately distended. There was diffuse tenderness, most marked in the left lower quadrant, and peristalsis was absent. Liver dulness appeared to be normal, and no fluid or masses could be made out. She was unable to lie flat in bed because of the abdominal spasm. Pelvic examination showed diffuse tenderness in both vaults. The fundus of the uterus could not be made out. There was exquisite tenderness on moving the cervix. Rectal examination showed tenderness with questionable bulging of the walls.

The temperature was 101.5°F., the pulse 120. The respirations were 20.

The urine examination was negative except for a very slight trace of albumin. The blood showed a red-cell count of 3,750,000 and a white-cell count of 29,700.

An x-ray of the abdomen showed the diaphragm high on both sides, although somewhat indistinct in outline because of hazy dulness in the lower lung fields. The costophrenic angles were shallow, and the upper lung fields were clear. The heart shadow was not remarkable. There was no evidence of free gas beneath the diaphragm.

During the two days following entry her temperature rose gradually to 104°F., and her pulse to 135. On the third day the nonprotein nitrogen of the blood was 22 mg. per cent, and the chlorides were equivalent to 99 cc. of N/10 sodium chloride. The white-cell count of the blood was 3300. She died on the fourth day.

Differential Diagnosis

Dr. John D. Stewart: When this patient was first seen she was not in shock, although she may have been after the onset of her abdominal pain, thirty-six hours previously. We see patients who, following the onset of an abdominal catastrophe, go into a state of shock which is compensated for during the subsequent day or two, only to recur perhaps as a terminal phenomenon. At the time of entry it is a perfectly good picture of peritonitis, there being nothing lacking to make the diagnosis.

Dr. George W. Holmes: This film was taken in the upright position and ought to show gas if present. The whole picture is that of a process below rather than above the diaphragm. The diaphragm is high, and its outline hazy. This might be extension of the inflammatory process to involve the diaphragm. I see no process in the chest to account for the haziness.

Dr. Stewart: Could it be taken as evidence of basal atelectasis?

Dr. Holmes: It might, but I doubt it.

Dr. Stewart: This is to me a very interesting picture. It involves the differential diagnosis of the acute abdomen. Time is short, so I will not attempt to go into the differential as fully as I otherwise might. It seems to me that the outstanding feature in the case on which we might base a diagnosis is sudden violent pain in a previously healthy person — a pain so severe that two doses of morphine and possibly sedatives by mouth were required to relieve it. Another important point is the rapid development of peritonitis, because I think it is fair to conclude that she died of general peritonitis. Another point of considerable interest to me is the fact that the gastrointestinal symptoms were minimal. She had reflex vomiting only immediately after the onset of the pain. She had no diarrhea, and passed no bloody material by rectum. Another very important point is the question of localization of tenderness. When you are confronted with such a picture as this, perhaps the most important point in making the diagnosis is localization of maximal tenderness, and that is often possible even in the presence of boardlike spasm and general tenderness. We are told that her maximum tenderness was in the lower abdomen, chiefly on the left, and a good deal is made of pelvic tenderness on pelvic examination. Those findings are probably very significant. Another interesting point is the shift in pain, which began in the epigastrium and subsequently was most marked in the lower abdomen. There are two questions that particularly come to one's mind in this case. One is why this patient was not operated on. It is possible that this was due to confusion in diagnosis and that when it became apparent that she had peritonitis it was considered better to treat her supportively. Another point of interest is the anemia, which apparently was real, — a red-cell count of 3,750,000, — if it is fair to assume it was not due to technical error.

In going over the differential diagnosis we can immediately exclude the extra-abdominal lesions which simulate acute abdomen. I do not believe this is coronary disease or diaphragmatic pleurisy or any of the other lesions above the diaphragm that produce abdominal symptoms. Likewise, I think we can exclude the urinary tract as the source of the symptoms. Then we are brought to the consideration of the classical trio of lesions which produce sudden severe abdominal pain in a previously healthy person, namely acute pancreatitis, perforation of a peptic ulcer and acute small-bowel intestinal obstruction. With perforation of peptic ulcer it is not necessary to have a history of dyspepsia preceding perforation. Twenty-five to 50 per cent of the cases in various series of cases

do not give such a history. In regard to the matter of gas beneath the diaphragm — free gas in the peritoneal cavity — the fact that the x-ray does not show any does not exclude the possibility of perforated ulcer. In about 50 per cent of the cases of perforated ulcer we do not succeed in demonstrating this sign. However, I think a perforated ulcer would not be my first diagnosis, particularly because the patient apparently had lower abdominal tenderness dominating the picture at the time of examination and because the pain was chiefly lower abdominal during her course in the hospital. To be sure, exudate can flow down into the pelvis and produce peritonitis in that region as well as in the rest of the abdomen, but in perforated peptic ulcer the predominating tenderness ought to be near the site of perforation and the spasm there should be more marked. Acute hemorrhagic pancreatitis produces violent pain and immediate shock and the course is often brief, as it was in this case. One of the striking features of acute hemorrhagic pancreatitis is persistent nausea and vomiting. We should also have some story of pain in the back, and tenderness should have been most marked over the region of the pancreas rather than in the left lower quadrant. Without going into that further, I shall pass that by as not being the most likely diagnosis, although it is a good possibility.

Acute obstruction of the upper intestine could produce as violent a picture as this with very severe pain. Torsion of the small bowel may lead to immediate prostration with subsequent peritonitis, if not corrected by operation. This patient vomited only once, according to the story, and the pain presently became lower abdominal rather than upper abdominal. Nevertheless, I believe that strangulation of a part of the intestine without complete occlusion is a possibility. Internal concealed hernia, or Richter's hernia, can give this picture and go on to peritonitis, but I feel that that probably is not the most likely diagnosis. Primary pelvic lesions I shall also pass over as being unlikely. To be sure twisted ovarian cyst can produce sudden abdominal pain and may lead to peritonitis, but I believe that the development of peritonitis would take longer than apparently was required in this case, and furthermore there is no note of any palpable mass in the pelvis on pelvic examination. Other pelvic lesions such as ruptured ectopic pregnancy seem very unlikely. So we are reduced to a consideration of some perforative lesion of the gastrointestinal tract, or possibly of the gall bladder, with a rapid development of peritonitis. The question of acute cholecystitis or plugging of the cystic duct with stone and subsequent rupture of the gall bladder would have to be considered. The attack of pain which she had had six weeks previously might have been on the basis of a cholecystitis. However it seems fair to expect that the examiner in the case would have detected greater tenderness in the abdomen in the region of the gall bladder and persistence of pain in the upper abdomen. Then there is the question of acute appendicitis with obstruction and possibly with fecalith in the lumen of the appendix. This would be a very unusual picture of acute appendicitis, but acute appendicitis is notable for its varied manifestations. We have seen patients operated on for perforated ulcer who have had obstructive appendicitis with perforation subsequent to the obstruction. In view of the predominance of tenderness and pain in the lower abdomen and particularly in view of the story of shift in pain from upper to lower abdomen I think that that is not an unreasonable diagnosis. There are unusual lesions which might produce the same picture: for example, perforation of an ulcer of a Meckel's diverticulum. Except for the fact that it is very rare, there is nothing wrong with making that diagnosis here.

I am unable to tie up the diagnosis with the anemia that the patient had unless she had had an ulcer in the gastrointestinal tract which had been bleeding and which subsequently ruptured. So I should say that this patient had diffuse peritonitis most likely following perforation of some part of the gastrointestinal tract, and that the appendix or a Meckel's diverticulum is as reasonable a source as any.

Dr. George W. W. Brewster: How about mesenteric thrombosis?

Dr. Tracy B. Mallory: Do you raise that as a possibility, or is that your diagnosis?

Dr. Brewster: I think it is possible.

Dr. Stewart: I had considered that in my own mind and discarded it because of the lack of gastrointestinal symptoms. Also, I doubt if a patient would live four or five days with as fulminating a process as that usually is.

Dr. Mallory: Of all the acute abdominal emergencies I think mesenteric thrombosis is the hardest to diagnose and the least often successfully diagnosed. That is what this patient had.

Clinical Diagnoses

Peritonitis, cause undetermined.
Bronchopneumonia.

Dr. Stewart's Diagnoses

General peritonitis from perforation of gastrointestinal tract.

Acute obstructive appendicitis?
Perforation of Meckel's diverticulum?

Anatomical Diagnoses

Mesenteric thrombosis, arterial and venous.
Gangrene of ileum.
Embolus to the superior mesenteric artery.
Thrombosis of right adrenal vein with hemorrhage into adrenal.
Arteriosclerosis: moderate, aortic, with mural thrombosis.
Peritonitis, acute focal.
Nephritis, chronic vascular.
Cortical adenoma of right adrenal.
Pulmonary congestion and edema.
Pleuritis, chronic fibrous, bilateral.
Leiomyomas of uterus.

Pathological Discussion

Dr. Mallory: The terminal ileum for the last three feet was acutely inflamed and gangrenous. The superior mesenteric artery was occluded by clots evidently originating in an embolus, and the source of the embolus was a mural thrombus in the aorta immediately above and partly around the mouth of the superior mesenteric artery itself. There was a secondary thrombosis of the superior mesenteric vein which looked fresher than the arterial one. It extended the whole length of the vein and a short way up the portal vein, and had begun to extend into the splenic vein. That, however, was very recent. There were no changes in the liver or spleen. We found nothing to account for the anemia. The diagnosis on the ward was general peritonitis, cause undetermined. They refused to guess.

The New England
Journal of Medicine
Formerly the
Boston Medical and Surgical Journal
Established in 1828

Owned by the Massachusetts Medical Society and Published under the Jurisdiction of the Committee on Publications

Official Organ of
The Massachusetts Medical Society
The New Hampshire Medical Society
The Vermont State Medical Society

Editorial Board

George G. Smith, M.D. — John P. Sutherland, M.D.
William B. Breed, M.D. — Stephen Rushmore, M.D.
George R. Minot, M.D. — Hans Zinsser, M.D.
Frank H. Lahey, M.D. — Benjamin White, Ph.D.
Shields Warren, M.D. — Henry R. Viets, M.D.
George L. Tobey, Jr., M.D. — Robert M. Green, M.D.
C. Guy Lane, M.D. — Charles C. Lund, M.D.
William A. Rogers, M.D. — John F. Fulton, M.D.
Dwight O'Hara, M.D. — A. Warren Stearns, M.D.

Associate Editors

Joseph Garland, M.D. — Thomas H. Lanman, M.D.
Donald Munro, M.D.

Walter P. Bowers, M.D., Editor Emeritus
Robert N. Nye, M.D., Managing Editor
Clara D. Davies, Assistant Editor

Subscription Terms: $6.00 per year in advance, postage paid, for the United States; Canada, $7.04 per year; $8.52 per year for all foreign countries belonging to the Postal Union.

Material for early publication should be received not later than noon on Saturday.

The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to the New England Journal of Medicine, 8 Fenway, Boston, Mass.

WHAT PRICE STANDARDS?

That there is a group of persons vigorously opposed to raising the standards of qualification for practicing the healing art in Massachusetts is shown by the number and character of the bills introduced for consideration by the General Court this year.

It was in May, 1936, that the governor signed the bill creating an Approving Authority for colleges giving premedical education and for medical schools, and the effective date for the beginning of this authority was then set by the statute as January 1, 1939. As that date draws near, renewed and intensive efforts are being made to bring to nought this legislation, which was designed to protect the people of the Commonwealth against improperly qualified practitioners of the healing art.

Nine bills have been introduced, the result, if not the intent, of which would be to expose the sick either to the risk of having continued the intolerably low standards of qualification for practice under which Massachusetts has suffered for decades and which other states have left far behind or, in some branches of the healing art, to the risk of having treatment by less qualified persons than are at present permitted to practice.

The first, House Bill 758, proposes to postpone the effective date of the beginning of the activity of the Approving Authority for three years, that is, from 1939 to 1942. The present provision gives over six years to schools in which to make the changes that are necessary in order to receive approval. The bill became a law in 1936, and the provisions do not apply to candidates matriculating before January 1, 1939. Since most medical students matriculate in September, the class entering in the fall of 1939 will be the first one affected. At that time only the first year of the school will have to be approved; in September, 1940, only the first and second years; in September, 1941, only the first, second and third years; and the whole four year course not until September, 1942. If any school is seriously preparing to meet the generally accepted standards and is at all likely to meet them, six years and four months would seem to be a generous allowance of time. If the schools are asking for nearly ten years, it is a fair question to ask whether they will use the time to try to change themselves or to change the statute. That someone, perhaps some school, seeks to change the statute, making it of no effect so far as it concerns institutions in Massachusetts, is shown by House Bills 1084, 1133, 1195 and 1341.

There are now four non-approved medical schools in the United States, of which two are in Massachusetts. Why should these be given special privileges? Why should the people of Massachusetts be especially exposed to the danger of poorly qualified practitioners? Under ordinary circumstances no other state will admit recent graduates of these two Massachusetts schools to practice within its borders.

There are two bills (Senate 282 and House 759) seeking to create a separate board of registra-

tion for osteopathic physicians. Why do osteopaths seek this separation? They now fulfill the same qualifications for examination as do graduates of regular medical schools, they take the same examinations, and if registered, they practice under the same conditions: they may operate, give drugs, practice obstetrics, sign death certificates. They are eligible to sit on the Board of Registration in Medicine on exactly the same conditions as other physicians. What more can they possibly want? They ask for exactly the same rights and privileges, after registration, as other physicians possess, and they ask that all this be procured in an easier way. They want their own board to be the approving authority for their schools, in accordance with requirements which are notably and notoriously substandard. These bills represent an endeavor to escape from the jurisdiction of the Approving Authority, the creation of which the osteopathic profession opposed so vigorously in 1936. One of the bills (Senate 282) provides for registration without education, — high school, college or medical school, — without degree, and without examination.

Then there are the bills (House 854 and 1210) for the chiropractors and the magnetic healers. Both osteopathy and chiropractic, as such, are on the wane. They represent theories of the purely mechanical origin of all disease and are not to be classed with medical specialties which consider only a limited portion of the body and its functions. They treat any and all manifestations of disease in any part of the body as due to a single cause — the "osteopathic lesion," or a subluxation of the spine as determined by "chiropractic analysis." Materialism in its broadest sense is inadequate enough in explaining diseases of human beings, but when materialism is limited to mechanics, no one can take the theory too seriously. The magnetic healers are in a different class: they do not even claim an objective test of the power of magnetic healing. "I know I have the power of healing" seems to be the only test. As it would obviously be impossible for any individual or group of individuals to determine the presence of such a "gift" in another, it is difficult to comprehend how any board would be able to act in such a way as to eliminate those self-designated healers who are disillusioned.

What should be, what shall be, the attitude of the medical profession toward these practitioners of the healing art? There can be only one reasonable position: all persons who desire to treat the sick in Massachusetts should meet certain minimum standards of qualification as to age, moral character, education, and proficiency as tested by examination. These standards should be the same for all. When the standards of qualification are once met and the practitioner once registered, he should be free to employ such methods of treatment as his intelligence, his training and his conscience indicate.

What should be, what shall be, the attitude of the public toward lowering of standards of practice for the healing art? It should be opposed, and will be opposed if the medical profession, to which it still looks for enlightenment on medical matters, can inform it intelligently and persuasively wherein the danger lies and in what the danger consists. The members of the medical profession should meet this responsibility squarely and carry it manfully, instead of shrugging their shoulders and saying pityingly, "If the public wants and prefers quacks and ignorant fellows to treat its ailments, let it have what it wants." The physician has a social responsibility, which he must not shirk. All these bills are opposed by the Committee on State and National Legislation of the Massachusetts Medical Society. It is the duty of the district medical societies to send representatives to the legislative hearings in order to voice such opposition, and they should not fail.

The price of standards, ever higher standards, for the care of the sick and suffering is eternal vigilance and eternal warfare — unceasing warfare against prejudice and selfishness and greed and ignorance, against the debasing of standards for any cause — "ceaseless devotion to the cause of humanity."

* * *

The bills, with abbreviated titles, the legislative committees to which they have been referred, and the dates of the hearings, are as follows:

Senate 282 — An act establishing a board of examination and registration in osteopathy. Public Health, February 17.

House 758 — An act relative to the qualifications of applicants for registration as qualified physicians. Public Health, March 1.

House 759 — An act creating a board of examination and registration in osteopathy. Public Health, March 1.

House 854 — An act relative to the practice of chiropractic. Public Health, March 8.

House 1084 — An act to preserve the rights of graduates of educational institutions chartered by the Commonwealth of Massachusetts. State Administration, February 23.

House 1133 — An act providing for special examinations for graduates of certain Massachusetts educational institutions. Education, March 8.

House 1195 — An act requiring boards of registration and examination to examine certain applicants. Public Health, March 1.

House 1210 — An act creating a board of examination and registration to regulate the practice of magnetic healers. State Administration, February 18.

House 1341 — "An act to further regulate the conduct of examinations by boards of registration of graduates of institutions of learning." This bill has not been printed and the exact wording of the title has not been stated. Education, March 8.

PETTIFOGGING PETTY POLITICS

It is axiomatic that politics have no place in anything that concerns the health of the public. This is recognized by everybody except the less desirable type of politician.

Being necessarily intimately concerned with the health of the public in its more sensational aspects, the Boston City Hospital has always been the target for attacks by politicians. They have also tried to use its various departments as sources of reward for their creditor constituents. Such an attempt was made — early in its history — to control staff appointments. This, of necessity, failed and the staff has been completely free from such domination for a long time. Then the buying of supplies was tampered with. This too was corrected by impetus provided through the staff, a department of which exposed and forcibly stopped the sale of grossly infected low-grade milk. After the War it was notorious that the hiring and discharging of the lesser-paid employees rested in political hands, and the long, hard battle necessary to correct this evil has only recently been won. Finally, the custom of using hospital beds, private rooms and the services of the medical and surgical staffs not only without any monetary compensation but even without the small courtesy of a "thank you" has also been stopped. This vicious racket involved politicians, their families, friends, neighbors and constituents and led directly to overcrowding, the use of the hospital facilities by those not entitled to them, the giving of false addresses by patients, and a resulting lack of efficiency in the care that the legitimate patients required. With a strict enforcement of the rule requiring payment of hospital bills every two weeks in advance and a thorough skilled investigation before admitting all non-emergency cases, this source of petty plunder, like the staff, the purchase of supplies and the control of non-civil-service employees, has been rudely taken away.

Only the nursing school remains as a means of granting favors. It is to be presumed that the nurses have been immune from this sort of thing in the past because, in the first place, they were ladies and it is hard to bring oneself to include ladies in schemes of this sort, and in the second place, all politicians up to the present had too much self-respect to stoop to such measures for the mending of their political fences. However, times are hard, a new city administration is starting, and economies, including salary cuts, are in the air. Reports have it that grave evil has been done to the taxpayers by the reorganization of the nursing school at the Boston City Hospital. It is difficult to understand how a reorganization that aims only to increases nurses' education and nursing efficiency, and that has been effected after prolonged and meticulous investigation by men experienced in all phases of hospital administration, can do the taxpayers anything but good.

It is time to put a permanent stop to such insensate baiting. The question today is not whether the nursing school at the Boston City Hospital is run well or badly. That can be safely left to the Trustees and staff. The question rather is, Shall patients be subjected to less and poorer care than they have every right to expect because the administration of the hospital is to be hamstrung every time some minor holder of political office takes it into his head to get some publicity?

The answer can only be, No. The sooner and the more unequivocally the Trustees make that answer the more efficient will be the hospital, and the better the care and health of the Boston public—politicians included.

NATIONAL DEFENSE WEEK

Military medicine and civil medicine are so different that the practitioner flounders when the former is thrust upon him. Diagnosis and treatment en masse is entirely different from that in the office and home and cannot be learned in a few days—to say nothing of the paper work that is so exasperatingly puzzling.

All such things are brought to mind by National Defense Week, which, as usual, is being celebrated between February 12 and 22. It is sponsored by the Reserve Officers' Association to acquaint the public with the status and needs of national defense, and serves to drive home the point that the medical reserve officer in times of peace should take advantage of the courses that are made available to him for instruction in military medicine.

CORRECTION

In the paper by Wiggin and Tartakoff, entitled "The Use of Combined Pontocaine and Novocain for Spinal Anesthesia," which appeared in the January 27 issue of the *Journal*, the fifth line from the bottom in the second column on page 171, which reads, in part, "at a rate of 0.5 cc. per minute," should be changed to read "at a rate of 0.5 cc. per second."

MASSACHUSETTS MEDICAL SOCIETY

SECTION OF OBSTETRICS AND GYNECOLOGY

M. Fletcher Eades, M.D., *Secretary*
19 Bay State Road
Boston

Case History No. 59. Placenta Ablatio At Term

Mrs. W. B., a white woman, aged thirty-seven, in her twelfth pregnancy, was seen in the clinic on January 1, 1937, when two months pregnant.

A series of selected case histories by members of the section will be published weekly.

Comments and questions by subscribers are solicited and will be discussed by members of the section.

Her family history was essentially negative. Her past history was negative except for scarlet fever at fifteen years of age. Ten pregnancies and labors had been normal, and it was known that in the eleventh pregnancy the blood pressure had been normal and the urine had shown no albumin. Her periods had always been regular with a twenty-eight-day cycle, lasting five days without pain. Her last menses started on October 26, 1936, making the estimated date early in August, 1937.

Physical examination showed a well-developed and nourished woman. Her heart showed no enlargement; there were no murmurs. The hemoglobin was 90 per cent (Sahli), and the blood pressure was 116 systolic, 72 diastolic. The lungs showed no rales or dulness. The extremities were normal. Vaginal examination showed the uterus to be enlarged, consistent with her dates. Her urine showed a specific gravity of 1.008; there was no albumin or sugar, and no pus, blood or casts.

She was seen each month in the clinic until two weeks before the baby was due. At this time her blood pressure was found to be 176 systolic, 96 diastolic. There was no albumin in the urine. She was told to take plenty of rest, to restrict the intake of salt, to take a daily dose of Epsom salts and to return in one week. However, she did not return to the clinic.

On July 27, she entered the hospital at 1:45 a. m. with cramp-like abdominal pains occurring every three minutes, which had been present for one hour. Her temperature was 98.4°F., and her pulse 90. Uterine contractions were present but the fetal heart could not be heard. There was no discharge of blood or amniotic fluid. At 3:45 a. m. pains were harder, and a moderate amount of bloody discharge was present. At 5:00 a. m. bleeding was considerable in amount, the uterus was tender between contractions, and pain was continuously present. Her facies was pale and anxious, and her pulse was 100. Antepartum separation of the placenta was diagnosed. The membranes were ruptured artificially, and at 6:00 a. m. a mid-forceps extraction of a dead baby was easily performed; this was immediately followed by expulsion of the placenta and a large amount of dark blood, both fluid and clotted. As bleeding continued following the birth of the baby and the placenta, the uterus was thoroughly packed with gauze, and 1 cc. Ergometrine given intravenously.

For a while following this treatment, bleeding seemed under control; but the uterus did not contract satisfactorily, and by 7:35 a. m. she was bleeding through the packing, and the uterine fundus felt extremely boggy. At this time she showed signs of shock, with marked pallor and restlessness, a pulse of 150, and a blood pressure of 70

systolic. Morphine (1/6 gr.) and Pituitrin (1 cc.) were given hypodermically, the foot of the bed was raised, she was grouped for transfusion, and salt solution was started by the intravenous route, running slowly so that she had 2,000 cc. in one hour. At 8:30 a. m. her condition was unimproved; the vaginal flow was pinkish instead of red, but still continuous. Transfusion of 500 cc. of citrated blood was given, followed by continuous, slow, intravenous salt solution. Morphine (1/6 gr.) hypodermically was again necessary. An improvement in color and pulse followed the transfusion, the pulse dropping to 128. For a while she rested peacefully. At 9:15 a. m. steady flowing again showed; this time it was bright red. She again became very pale, and the pulse became thready and uncountable.

It was apparent that the uterus did not have the power of contracting sufficiently to stop the bleeding and that she would die from hemorrhage unless it was checked. Hysterectomy was the only measure available, although it seemed impossible for her to stand the shock of operation. It was determined, however, to take the risk of operative shock, as it seemed her only chance of recovery.

At 10:00 a. m. another transfusion of 500 cc. of citrated blood was started, the uterine packs were removed, and a supravaginal hysterectomy was performed under light ether anesthesia. The uterus was bluish black throughout most of its external surface, and the coloring extended into both broad ligaments and down onto the bladder peritoneum. On cutting the uterus, the entire wall was invaded by dark blood over a large part of the anterior and posterior uterine walls. Slow administration of intravenous salt solution followed the transfusion. Her color and pulse again improved during transfusion, the pulse dropping to 140; the blood pressure was 80 systolic. She was returned to bed with a pulse of 130 and a blood pressure reaching 100 systolic, 60 diastolic. Salt solution (1000 cc.) was given.

Recovery from the shock of hemorrhage and operation was fairly good. She showed a hemoglobin percentage of 45 on the following day and was given another transfusion of 500 cc. of citrated blood. She took fluids well, but it was noticed that in the next few days her urinary output was very small. A catheter specimen of urine on July 29 showed a specific gravity of 1.009, a slight trace of albumin, no sugar and a sediment containing many red-blood cells, an occasional white-blood cell and a few granular casts. The plasma protein of her blood was below the critical level of 5 gm. per cent. Her blood pressure varied from 120 to 150 systolic, 70 to 80 diastolic. Her pulse ranged from 80 to 100, and her temperature from 99 to 100°F. On July 29 she was given 300 cc. of citrated blood, and her intake of fluid was decreased on account of the low blood protein and the small amount of urine.

On July 30 she seemed stronger; her intake and output of fluids were more nearly balanced. She showed no signs of edema and no rales in the lungs but had headache at times.

On July 31 she complained of severe headache, dizziness and epigastric pain; her blood pressure was 165 systolic and 80 diastolic. In the late afternoon she became confused, and had convulsive movements of her right arm and both legs with a generalized convulsion lasting five minutes, following which she was perfectly conscious. During the night she had six similar convulsions with partial consciousness between. There was no paralysis or disturbance of reflexes between convulsions. Her blood pressure varied from 150 to 180 systolic, 90 to 105 diastolic. She voided 450 cc. of urine showing a little albumin, many blood cells and a few granular casts. Her retinas showed no exudate, hemorrhage or abnormality of the arteries.

Treatment during the convulsive period consisted of morphine once, followed by magnesium sulfate (20 per cent) subcutaneously, in 10 cc. doses intravenously at three-hour intervals for three doses. Lumbar puncture was done, dropping the spinal fluid pressure from 250 to 150 mm. of water. This fluid showed no abnormalities. She was also given 100 cc. of 50 per cent glucose intravenously twice.

On the following morning she was conscious and somewhat nervous but had no more convulsions. Her urine amounted to 20 cc., with findings as before; her blood pressure was 140 systolic, 70 diastolic. The blood urea nitrogen was 70 mg. per cent.

Daily thereafter she showed steady improvement, passing normal amounts of urine and with a blood pressure varying from 145 to 160 systolic, 90 to 100 diastolic. On August 10 her blood urea nitrogen was 42 mg. and her hemoglobin 55 per cent. She made a normal surgical convalescence from her laparotomy. She was discharged home with instructions to rest in bed, take iron and follow a low-protein diet. Her urine at this time showed a specific gravity of 1.005, no albumin or sugar, and nothing in the sediment.

On November 4, several months after labor and operation, she was seen at the clinic with the following results: her hemoglobin was 90 per cent; her blood pressure 164 systolic, 110 diastolic; heart normal; blood urea nitrogen 25 mg. per cent; phenolsulfonphthalein 45 per cent in two hours.

Her catheterized urine showed a specific gravity, after fluid restriction, of 1.008, no albumin or sugar, and a sediment containing about 10 red-blood cells and leukocytes per high-power field. Her retinas showed no exudate or narrowing of the arteries. Her general condition was very satisfactory.

Comment. In reviewing the case, several important facts are evident.

There was a failure in prenatal treatment, in that following the discovery of hypertension she did not have careful enough treatment. She should have entered the hospital or at least have been seen more frequently.

Very extensive hemorrhage both into the uterine cavity and into the uterine musculature was present, and as a result, the uterine musculature lost its power of contracting so that bleeding did not cease with the birth of the child or with careful packing of the uterine cavity.

Thorough and persistent administration of intravenous salt solution and blood undoubtedly saved her from death and enabled her to stand the shock of hemorrhage and hysterectomy, the latter being the only measure effective in checking the bleeding.

The late occurrence of convulsions, associated with a high degree of uremia, suggests the presence of chronic nephritis, with the uremia possibly precipitated by the previous hemorrhage or treatment. The subsequent final examination confirms the opinion that she had an underlying chronic nephritis, the exact type of which still remains in doubt.

NOTICE TO FELLOWS OF THE MASSACHUSETTS MEDICAL SOCIETY

THE *New England Journal of Medicine* is sent to all fellows whose dues are fully paid. After March 1, delinquent fellows are dropped from the mailing list. All fellows are urged to remit their dues for the current year to their district treasurers before March 1.

CHARLES S. BUTLER, M.D., *Treasurer.*

MEDICAL POSTGRADUATE EXTENSION COURSES

The following sessions, given by the Massachusetts Medical Society in co-operation with the Massachusetts Department of Public Health, the United States Public Health Service and the Federal Children's Bureau, have been arranged for the week beginning February 21:

BRISTOL NORTH

Thursday, February 24, at 4:00 p. m., at the Morton Hospital, Taunton. Subject: Pneumococcus Pneumonia and Serum Therapy. Instructor: Frederick T. Lord. Arthur R. Crandell, *Chairman.*

BRISTOL SOUTH (New Bedford Section)

Friday, February 25, at 4:00 p. m., at St. Luke's Hospital, New Bedford. Subject: Complications in Obstetrics Illustrated by Case Histories. Instructor: Raymond S. Titus. Robert H. Goodwin and Howard P. Sawyer, *Chairmen.*

ESSEX SOUTH

Course omitted this week on account of Washington's Birthday.

MIDDLESEX EAST

Course omitted this week on account of Washington's Birthday.

MIDDLESEX NORTH

Friday, February 25, at 7:00 p. m., at St. John's Hospital, Lowell. Subject: Gonorrhea in the Male. Instructor: Oscar F. Cox, Jr. William S. Lawler, *Chairman.*

NORFOLK

Friday, February 25, at 8:30 p. m., at the Norwood Hospital, Norwood. Subject: Bleeding in the Last Trimester of Pregnancy. Instructor: Raymond S. Titus. Hugo B. C. Riemer, *Chairman.*

NORFOLK SOUTH

Monday, February 21, at 8:30 p. m., at the Quincy City Hospital, Quincy. Subject: The Use and Misuse of Prontylin. Instructor: R. Cannon Eley. David L. Belding, *Chairman.*

PLYMOUTH

Course omitted this week on account of Washington's Birthday.

WORCESTER (Milford Section)

Thursday, February 24, at 8:30 p. m., in the Nurses' Home of the Milford Hospital, Milford. Subject: Drug Therapy in Pediatrics. Instructor: Eli C. Romberg. Joseph Ashkins, *Chairman.*

WORCESTER NORTH

Friday, February 25, at 4:30 p. m., at the Burbank Hospital, Fitchburg. Subject: The Use and Misuse of Prontylin. Instructor: Benjamin W. Carey, Jr. Edward A. Adams, *Chairman.*

MISCELLANY

OPPORTUNITY FOR PHYSICIANS TO TOUR AMERICA EN ROUTE TO THE SAN FRANCISCO MEETING

The thought that the forthcoming American Medical Association session in San Francisco, June 13 to 17, is such a splendid opportunity for a tour of the United States, both going out and coming back, has inspired definite action. The co-operation of more than twenty-five state medical societies has made it possible to arrange a special train tour which will include such outstanding high lights of the North American continent as the Indian Detour, the Grand Canyon, Los Angeles, Riverside and Santa Catalina Island — on the way out to San Francisco. A choice of two return routes is possible, one of which

visits the charming cities of Portland, Seattle, Victoria and Vancouver and the beautiful scenic spots of the Canadian Rockies; the second route travels via Yellowstone National Park, Salt Lake City, Royal Gorge, Colorado Springs and Denver.

There is an all-inclusive price for this tour which includes transportation from home-town to home-town, though the tour starts officially at Chicago on Monday, June 6, from which point an American Express escort joins the group, as this travel company has been appointed transportation agent and the business details of the trip are in its capable hands.

Let us take a preview of the tour. The first day out of Chicago, racing across the broad, wheat-growing face of Kansas, we become acquainted with our traveling companions, physicians from other states, their families and friends, and find ourselves among congenial, like-minded people. We first leave our train at Lamy, New Mexico, to enter the Indian pueblo district by motor-coach. We spend a whole day exploring the traces left by a vanished civilization on this continent, visiting Santa Fe, Tesuque, Puye and Santa Clara Pueblo.

The next morning's arrival at the Grand Canyon will remain in our memories forever. The vast chasm, from four to eighteen miles wide from rim to rim, gives us stupendous vistas of awe-inspiring beauty, unparalleled the world over. We drive over the famous Hermit Rim Road, skirting the edge of the chasm in the morning, and in the afternoon over the Desert View Road through the Tusayan National Forest and along the canyon's rim, stopping at Yavapai Point Observation Station for a short, interesting lecture by the park naturalist. This drive ends at the Watch Tower, a re-creation of the ancient towers erected by the prehistoric inhabitants of the Southwest.

The amazing city of Los Angeles is next on our itinerary, and our sightseeing trips acquaint us with its Spanish quarter and Chinatown, as well as its beautiful environs, including flowering Pasadena. Riverside, with its orange empire, lemon and grapefruit orchards, and famous Mission Inn, is another destination; and then, on our third day in California, we sail to beautiful Santa Catalina Island, playground of this land of the sun. And in this delightful manner, a week after leaving Chicago, we arrive at San Francisco in time for the meeting. We shall not discuss the interesting time that awaits us at our conclaves, as the object of this article is to describe the pre- and postconvention tour. So we consider our return itinerary.

Supposing we had chosen Return Route No. 1. We shall visit Portland, Oregon, famed as the City of Roses, and enjoy a drive along the noted Columbia River Highway. Seattle is next, and here we also cover all the points of interest, including both the lake and sound districts. Now the Canadian part of our journey begins; we sail by comfortable steamer to the cities of Victoria and Vancouver, where we do sightseeing. Now a train takes us into the enchanting scenic region of the Canadian Rockies, and we stop at Chateau Lake Louise, at the lake of the same name —a gem of exquisite color, surrounded by green forests and snowy peaks. Our drives through the heart of the Rockies take us to Moraine Lake, the Valley of Ten Peaks, Johnson Canyon and finally to Banff, where we make another stopover. After additional sightseeing around Banff, we entrain for Chicago.

Return Route No. 2 takes us to Chicago in a more southerly route. A three-and-a-half-day tour of Yellowstone National Park is one of the high lights of this tour. Ranger naturalists conduct our party to the geysers and hot pools, and we feast our eyes on Old Faithful in its hourly eruption. We also see the Grand Canyon of the Yellowstone and Mammoth Hot Springs. Salt Lake City is on our itinerary, which gives us an opportunity to visit Saltair Beach on Great Salt Lake, also the great copper mills and smelters. Our next call is at Colorado Springs, the noted health and pleasure resort. Our travels in the Rockies take us up to the summit of Pikes Peak, to the Garden of the Gods, to Seven Falls, and finally to Denver. This lovely city is a center for outings in the Rockies, and we are soon off on a sixty-five-mile tour of Denver mountain parks, including the memorial museum and tomb of Buffalo Bill of western fame. From Denver we travel to Chicago.

The above is barely a glimpse of the outline of the tours, but it is hoped that some idea has been given of the enjoyable travel awaiting those physicians and their families and friends, who wish to combine attendance at the meeting with an interesting journey and a happy vacation.

PRIZE SUBSCRIPTION

The *Journal* is offering a prize subscription for one year to the undergraduate contributing the best original article to the *Tufts College School of Medicine Medical Journal* during the current year. The award will be made annually. The editorial staff of the *Journal* will make the final selection from three papers recommended by the Tufts faculty advisers.

CORRESPONDENCE

SUGGESTED INSTRUCTIONS CONCERNING THE USE OF SULFANILAMIDE

To the Editor: Some time ago three members of the hospital staff were requested by the General Executive Committee of the Massachusetts General Hospital to submit suggestions concerning the use of sulfanilamide. Their report was so comprehensive and clear that copies were made and forwarded to all staff members. A copy is enclosed in the hope that it may be of interest and value to readers of the *Journal.*

N. W. Faxon, M.D., *Director.*

Massachusetts General Hospital,
Boston.

* * *

I. *Drugs to be used.* Sulfanilamide (Merck).
Prontylin (Winthrop Chemical Company).
Prontosil (Winthrop Chemical Company), rarely.

II. *Diseases in which it should be employed.*
1. Gonococcal infections, particularly arthritis.
2. Meningococcal infections, particularly meningitis.
3. Acute or subacute infections due to beta hemolytic streptococci.
4. The drug is still to be regarded as under trial for Type III pneumococcus, *B. coli, B. proteus, B. welchii* and *B. typhosus.*

Whether or not all cases of chronic prostatitis due to the gonococcus can be cared for with sulfanilamide remains to be seen. We have observed a few failures. They may represent inadequate therapy. Time will tell.

III. *Dosage.* Until we have further information concerning the smallest amount of the drug necessary to cure any of the above-mentioned infections, it would seem wisest to prescribe the

drug in full doses. Full doses are calculated as follows: ¾ gr. per pound of body weight, not exceeding 120 gr. in any 24-hour period. The exact length of time such treatment must be continued is unknown; probably 1 or 2 weeks of such therapy is adequate.

IV. *Method of giving.* It is preferable to administer the drug by mouth. The daily calculated dose should be subdivided into four or six equal parts and given at 6- or 4-hour intervals. In rare instances, when the patient seems to be in immediate danger of death, it may be advisable to give the full dose at once, or half the full dose at the beginning of treatment and the other half 4 hours later. The patient should then go on to a fourth and sixth of the full dose at 6- or 4-hour intervals.

Sodium bicarbonate may be given in equal doses with each dose of sulfanilamide, if desired. The soda has no known effect upon the pharmacologic action of the drug and may allay the severity of the gastric symptoms and prevent the acidosis attendant upon the use of sulfanilamide.

If the patient is vomiting, a 0.6% solution of sulfanilamide (Merck) in saline may be autoclaved and given subcutaneously as a clysis, or if desired, Prontosil may be injected intramuscularly.

V. *Suggested laboratory studies.*

1. A complete blood examination should be done before starting the drug and should be repeated every 3 to 7 days.
2. If there is any question of renal impairment or of acidosis, nonprotein nitrogen, chloride and carbon-dioxide-combining-power determinations should be done on blood samples and should be repeated, as seems indicated, in order to evaluate renal function and the degree of acidosis.
3. Blood sulfanilamide determinations are not absolutely necessary. The maximum blood value is probably attained between 24 and 72 hours after the institution of therapy. Therefore, such a determination made during this period and repeated occasionally should give one an excellent idea as to the existing blood concentration. From the data at hand, it would appear that the blood level should be maintained at 5 mg. per 100 cc. or above. On full doses, most patients vary between 8 and 15 mg. free sulfanilamide per 100 cc. of blood. Excessive fluid intakes tend to decrease the blood-sulfanilamide level, and therefore it is probably wise not to administer fluids excessively; a total 24-hour fluid intake of from 2000 to 3000 cc. would seem adequate.

VI. *Contraindications.*

1. Severe anemia and leukopenia.
2. Marked renal impairment.
3. Obstructive jaundice.

VII. *Incompatible drugs.* No type of sulfate medication, such as magnesium sulfate, ferrous sulfate, and so forth, should be administered during the time the patient is receiving sulfanilamide because it increases the incidence of sulfhemoglobinemia.

VIII. *Complications.*

1. Cyanosis. Sulfhemoglobinemia is the most frequent cause, but actual discoloration of the cells may account in part for the cyanosis.
2. A moderate acidosis is encountered in a fair number of the patients receiving the drug; rarely does the carbon-dioxide-combining power of the blood drop below 40 vol. per cent.
3. Gastric symptoms are frequent, although rarely severe. They usually consist of nausea and loss of appetite; vomiting is occasionally encountered.
4. Various skin eruptions as well as urticaria have been encountered. The exact manner in which these are produced is unknown. When present, the drug should probably be discontinued.
5. Sustained fever as high as 103 or 104°F. may be encountered during the administration of the drug. It disappears promptly on discontinuance of it.
6. Hemolytic anemia has been observed. Anemia is frequently encountered, and varying grades of leukopenia have been seen. The leukopenia may appear after the discontinuance of the drug.

   Severe anemia is a contraindication to further use of the drug.
7. A rising blood nonprotein nitrogen should be considered as a possible contraindication to further use of the drug.

WALTER BAUER, M.D.,
CHAMP LYONS, M.D.,
E. ROSS MINTZ, M.D.

ARTICLES ACCEPTED BY THE AMERICAN MEDICAL ASSOCIATION COUNCIL ON PHARMACY AND CHEMISTRY

To the Editor: In addition to the articles enumerated in our letter of January 12 the following have been accepted:

Abbott Laboratories
- Brucella Melitensis Bacterin — Abbott
- Bismuth Subsalicylate with Butyn-D.R.L., 30 cc. bottle
- Bismuth Subsalicylate with Butyn-D.R.L., 500 cc. bottle
- Dextrose 20% W/V in Distilled Water
- Dextrose, U.S.P., 25% W/V in Physiological Sodium Chloride Solution
- Dextrose 2½% in Physiological Sodium Chloride Solution
- Metaphen Ophthalmic Ointment

B. L. Benson
- Glycyrrhiza Compound Extract Squares

International Vitamin Corporation
- I.V.C. Cod Liver Oil Concentrate Capsules
- I.V.C. Cod Liver Oil Concentrate in Oil

Lederle Laboratories
- Rabies Vaccine — Lederle (Semple Method), 7 vials package

Eli Lilly & Co.
- Combined Diphtheria Toxoid-Tetanus Toxoid-Alum Precipitated, one 5 cc. vial package

Mallinckrodt Chemical Works
- Sulfanilamide — Mallinckrodt

Mead Johnson & Co.
Mead's Compound Syrup Oleum Percomorphum
Merck & Co., Inc.
Vinethene (Merck), three 10 cc. bottles package
Parke, Davis & Co.
Staphylococcus Toxoid
Solution Adrenalin Chloride 1:100
E. R. Squibb & Sons
Ampule Sterile Solution Procaine Hydrochloride — Squibb, 10 per cent, 2 cc.
Winthrop Chemical Co., Inc.
Pontocaine Hydrochloride Tablets, 0.1 gm.

PAUL NICHOLAS LEECH, *Secretary.*

535 North Dearborn Street,
Chicago, Illinois.

RECENT DEATH

HOPKINS — BERTRAND H. HOPKINS, M.D., of 24 Washington Street, Ayer, Massachusetts, died August 13, 1937. He was in his fifty-sixth year.

Dr. Hopkins received his degree from Tufts College Medical School in 1897.

He was a fellow of the Massachusetts Medical Society and a member of the American Medical Association.

REPORT OF MEETING

BOSTON UNIVERSITY MEDICAL SOCIETY

"Observations on the Diagnosis and Treatment of Brain Tumors" was the subject of an address given by Dr. Gilbert Horrax of the Lahey Clinic before the monthly meeting of the Boston University Medical Society on February 7 in the Evans Memorial Auditorium. Dr. Reginald Fitz presided at the meeting.

The student officers of the society are: president, Robert E. Moss, Boston; vice-president, John P. Rattigan, Hyde Park; corresponding secretary, Timothy L. Curren, Dorchester; secretary, Marion V. Zottoli, Dorchester; regional delegates, Nicholas Fiumara, Boston, Deborah V. Rubenstein, Roxbury, and Frederick J. Fagan, Norwich, Connecticut; forum committee, Sidney Gohn, New York City, Morris Taylor, Chelsea, John Dougherty, Bath, Maine, Iver S. Ravin, Brookline, and Isabel S. Money, Mattapan.

NOTICES

CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS, UNDER THE PROVISIONS OF THE SOCIAL SECURITY ACT

CLINIC	DATE	ORTHOPEDIC CONSULTANT
Haverhill	March 2	Arthur T. Legg
Lowell	March 4	Albert H. Brewster
Salem	March 7	Harold C. Bean
Gardner	March 8	Mark H. Rogers
Brockton	March 10	George W. Van Gorder
Springfield	March 16	Garry deN. Hough, Jr.
Worcester	March 18	John W. O'Meara
Pittsfield	March 21	Francis A. Slowick
Hyannis	March 22	Paul L. Norton
Fall River	March 28	Eugene A. McCarthy

UNITED STATES CIVIL SERVICE EXAMINATION

Physiotherapy Aide, $1,800 a Year

Applications must be on file with the United States Civil Service Commission at Washington, D. C., not later than March 7.

Applicants must have been graduated from a school of physiotherapy meeting the standards established by the American Medical Association, or they must have had at least eighteen months' experience as classified pupil aides in physiotherapy in a Veterans' Administration facility.

CARNEY HOSPITAL

The monthly clinical meeting and luncheon of the Carney Hospital staff will be held on Monday, February 21, at 11:30 a. m., in the Andrew Carney Assembly Hall.

PROGRAM

Case Report: Compound fracture of skull with convulsions, decompression and recovery. Dr. W. E. Browne.
Pathology Exhibit.
Fluid Balance. Dr. T. J. P. Lyons.

Discussion by Dr. N. A. Welch, Dr. C. A. Robinson and Dr. John Thornton.

Physicians and medical students are cordially invited to attend.

R. J. HEFFERNAN, M.D., *Secretary.*

NORFOLK DISTRICT MEDICAL SOCIETY

The next regular meeting of the Norfolk District Medical Society will be held in the Beth Israel Hospital, on Wednesday evening, February 23, at 8:15.

PROGRAM

Business.
Communication: Dermatitis venenata due to cosmetic and industrial irritants. Dr. John G. Downing. Discussion by Dr. Francis P. McCarthy.
Collation.

FRANK S. CRUICKSHANK, M.D., *Secretary.*

ROBERT B. BRIGHAM HOSPITAL

There will be an open meeting at the Robert B. Brigham Hospital, 125 Parker Hill Avenue, Boston, on Thursday evening, February 24, at 8:15. Dr. Maurice B. Strauss will speak on "Vitamin Deficiencies."

Doctors and medical students are cordially invited to attend.

ROBERT SANDERSON, M.D., *Secretary.*

TRUDEAU SOCIETY

The next meeting of the Trudeau Society will be held in the auditorium of the Beth Israel Hospital on February 24, at 8:15 p. m. Dr. Evarts A. Graham, editor of the *Journal of Thoracic Surgery* and professor of surgery at Washington University School of Medicine, will speak on "The Problem of Bronchiogenic Carcinoma." The paper will be discussed by Dr. Edward D. Churchill and Dr. Richard H. Overholt.

MOSES J. STONE, M.D., *Secretary.*

BOSTON MEDICAL HISTORY CLUB

There will be a meeting of the Boston Medical History Club at the Boston Medical Library, 8 Fenway, Boston, on Wednesday, February 23, at 8:15 p. m.

Dr. Chester M. Jones will speak on "The Development of Our Knowledge of the Gastrointestinal Tract and Its Diseases."

BENJAMIN SPECTOR, M.D., *Secretary.*

NEW ENGLAND SOCIETY OF PSYCHIATRY

The annual spring meeting of the New England Society of Psychiatry will be held at the Neuro-Psychiatric Institute of the Hartford Retreat, Hartford, Connecticut, on April 26.

GEORGE A. ELLIOTT, M.D., *Secretary-Treasurer.*

BOSTON SOCIETY FOR THE ADVANCEMENT FOR GASTROENTEROLOGY

The Boston Society for the Advancement of Gastroenterology will hold a meeting in the amphitheater of the new surgical building of the Boston City Hospital, on Thursday, February 24, at 12 o'clock noon. Dr. Maurice Binet will lecture on "Liver Deficiencies." Dr. Binet is chief physician at Vichy and a medical doctor at the Faculty of Paris.

C. W. MCCLURE, M.D., *Secretary.*

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING MONDAY, FEBRUARY 21

MONDAY, FEBRUARY 21

*11:30 a. m. Carney Hospital, monthly clinical meeting and luncheon. Andrew Carney Assembly Hall.

WEDNESDAY, FEBRUARY 23

*9-10 a. m. Boston Dispensary. Hospital case presentation. Dr. S. J. Thannhauser.

*12 m. Cliincopathological conference. Children's Hospital Amphitheater.

8:15 p. m. Norfolk District Medical Society. Beth Israel Hospital, Boston.

8:15 p. m. Boston Medical History Club. Boston Medical Library. 8 Fenway.

THURSDAY, FEBRUARY 24

8:30-9:30 a. m. Exchange visit, surgical and orthopedic staffs of the Peter Bent Brigham and Children's hospitals, held this week at the Peter Bent Brigham Hospital.

*9-10 a. m. Boston Dispensary. Gastrointestinal clinic. Dr. K. S. Andrews.

12 m. Boston Society for the Advancement of Gastroenterology. Boston City Hospital. Amphitheater of the new surgical building.

8:15 p. m. Trudeau Society. Beth Israel Hospital auditorium, Boston.

*8:15 p. m Robert B. Brigham Hospital. 125 Parker Hill Avenue, Boston.

FRIDAY, FEBRUARY 25

*9-10 a. m. Boston Dispensary. The Diagnosis of Multiple Myeloma. Dr. Bernard Jacobson.

*10 a. m. - 12:30 p. m. Tumor clinic. Boston Dispensary.

8 p. m. Massachusetts Psychiatric Society. Boston Psychopathic Hospital.

SATURDAY, FEBRUARY 26

*9-10 a. m. Boston Dispensary. Hospital case presentation. Dr. S. J. Thannhauser.

*10 a. m. - 12 m. Staff rounds at the Peter Bent Brigham Hospital. Conducted by Dr. Henry A. Christian.

SUNDAY, FEBRUARY 27

4 p. m. Illustrated, public, health lecture, Faulkner Hospital auditorium. Backache. Dr. John D. Adams.

4 p. m. Free public lecture. Harvard Medical School, amphitheater of Building D. Pain in the Abdomen. Dr. Channing Frothingham and Dr. Richard H. Miller.

*Open to the medical profession.

FEBRUARY 17 — Boston Society of Psychiatry and Neurology, Boston Medical Library, 8 Fenway, at 8:15 p. m.

FEBRUARY 17 — New England Pathological Society, amphitheater of Mallory Institute of Pathology, Boston City Hospital, 8 p. m.

FEBRUARY 21 — Carney Hospital. Page 321.

FEBRUARY 22 — New York University College of Medicine. Alumni Day. Page 245, issue of February 3.

FEBRUARY 23 — Boston Medical History Club. Page 321.

FEBRUARY 24 — Boston Society for the Advancement of Gastroenterology. Notice above.

FEBRUARY 24 — Trudeau Society. Page 321.

FEBRUARY 24 — Robert B. Brigham Hospital. Page 321.

FEBRUARY 25 — Massachusetts Psychiatric Society. Page 245, issue of February 3.

MARCH 1 — Greater Boston Medical Society. Beth Israel Hospital auditorium, 8:30 p. m.

MARCH 3 — George Washington Gay Lecture. Page 245, issue of February 3.

MARCH 10 — Pentucket Association of Physicians. Hotel Bartlett, 95 Main Street, Haverhill, 8:30 p. m.

MARCH 10, 11, 12 — New England Hospital Association. Page 51, issue of January 6.

MARCH 28 - APRIL 1 — Postgraduate Institute of the Philadelphia County Medical Society. Page 282, issue of February 10.

APRIL 4-8 — The American College of Physicians. Page 41, issue of July 1.

APRIL 26 — New England Society of Psychiatry. Notice above.

MAY 31, JUNE 1 and 2 — Annual meeting of the Massachusetts Medical Society. Hotel Bradford, Boston.

JUNE 13-17 — American Medical Association. San Francisco.

JUNE 13, OCTOBER 8 and NOVEMBER 15 — American Board of Ophthalmology. Page 282, issue of February 10.

OCTOBER 17-21 — Clinical Congress of the American College of Surgeons. New York City.

DISTRICT MEDICAL SOCIETIES

BRISTOL SOUTH

MAY 5 — 5 p. m., New Bedford.

ESSEX SOUTH

MARCH 2 — Lynn Hospital. Clinic at 5 p. m. Dinner at 7 p. m. Speaker and subject to be announced.

APRIL 6 — Gloucester Hospital, Gloucester. Clinic at 5 p. m. Dinner at 7 p. m. Speaker and subject to be announced.

MAY 5 — Censors meet at Salem Hospital, 3:30 p. m.

MAY 11 — Annual meeting, Salem Country Club, Peabody. Dinner at 7 p. m. Speaker and subject to be announced.

FRANKLIN

Meetings will be held at the Franklin County Hospital, Greenfield, at 11 a. m. the second Tuesdays of March and May.

HAMPDEN

Meetings will be held on the fourth Tuesday in April and July.

MIDDLESEX EAST

Meetings will be held at the Bear Hill Golf Club, Stoneham, at 12:15 p. m. on March 16, and May 11.

MIDDLESEX NORTH

Meeting will be held at the Vesper Country Club, Lowell, on April 27.

NORFOLK DISTRICT

FEBRUARY 23 — Page 321.

MARCH 29 — Hotel Kenmore. 8:15 p. m. Subject to be announced but to be related to diseases of the kidney. Dr. Albert A. Hornor.

MAY — Annual meeting.

The censors meet on the first Thursdays of May and November in each year.

NORFOLK SOUTH

Meetings held at 12 noon.

MARCH 3 — Norfolk County Hospital, South Braintree.

APRIL 7 — At the Quincy City Hospital.

MAY 5 — Annual meeting.

PLYMOUTH

Meetings will be held at 11 a. m. on March 17, April 21, May 19 and July 21.

SUFFOLK

MARCH 15 — Joint meeting with Boston Obstetrical Society.

WORCESTER

At the following meetings, except the annual meeting, dinner will be at 6:15, to be followed by business session and scientific program.

MARCH 9 — Memorial Hospital, Worcester.

APRIL 13 — Hahnemann Hospital, Worcester.

MAY 11 — Afternoon and evening, annual meeting. Place and schedule of program to be announced.

BOOKS RECEIVED FOR REVIEW

Love and Happiness: Intimate problems of the modern woman. I. M. Hotep. 235 pp. New York and London: Alfred A. Knopf, 1938. $2.00.

Fever Therapy: Abstracts and discussions of papers presented at the First International Conference on Fever Therapy, March 29, 30, 31, 1937. Walter M. Simpson, William Bierman, et al. 486 pp. New York: Paul B. Hoeber, Inc., 1937. $5.00.

BOOK REVIEWS

A Bibliography of the Works of Ambroise Paré: Premier Chirurgien & Conseiller du Roy. Janet Doe. 266 pp. Chicago: The University of Chicago Press, 1937. $5.00.

Miss Doe has written a very valuable book. It is much more than a bibliography, for she has listed with extraordinary accuracy not only every known edition of Paré's works, but, in describing these books, she has added notes of unusual value on the author's life and on the times. She points out, for instance, that Paré was a man of great versatility; that he began as an unlearned barber surgeon and rose to be the idol of the army surgeons of France, and surgeon to the French kings for nearly forty years. Although he is best known for his rejection of boiling oil for the treatment of wounds and the use of the ligature and of podalic version, he is equally the epitome of Renaissance surgery, for in his simple and kindly manner, in spite of his being at times vain and ambitious, Paré brought common sense to surgery and took away from it the muddy thinking of the Middle Ages. Although at first unlearned as a writer, his style grew with him, and his later books, published after 1560, were well written. Miss Doe writes that "his realistic story of the siege of Metz can fearlessly be compared with the greatest narratives of history. The golden thread running through it all is the personality of the author." Much of interest in regard to the man will therefore be found in this splendid book.

The bibliography is unusually complete. Miss Doe has searched for copies of the various editions and works in libraries throughout the world with unusual pertinacity. She has also ascertained the number of copies in the hands of private collectors. Foremost among these is Dr. Harvey Cushing, whose unusual collection was used as the basis for most of the descriptions written by Miss Doe. Each book is described in complete detail and in most cases the title page is reproduced; the copies used are indicated and also the number and location of all copies found. There is little to criticize in this splendid piece of research, the result of many years of effort by an extremely conscientious individual. Unfortunately, the faults, if any, fall upon the press. Much of the type is badly chosen, and the title pages are poorly reproduced. There are a number of criticisms in regard to the bibliographical style used by the author, but these are minor and relatively unimportant. With such splendid examples before her as the bibliographies issued in recent years by Geoffrey Keynes, particularly those of William Harvey and Sir Thomas Browne, it seems a little unfortunate that Miss Doe did not follow in detail the style set by her predecessor. In spite of these criticisms, which must be acknowledged as being definitely minor, except for the printing, the book is one of the outstanding bibliographies of our time and as such sets a standard that few will equal and practically none surpass.

Genital Abnormalities, Hermaphroditism, and Related Adrenal Diseases. Hugh H. Young. 649 pp. Baltimore: The Williams & Wilkins Co., 1937. $10.00.

This is an extraordinary book. Written by the author of one of the best textbooks of urology, it represents another outstanding achievement by Dr. Young. Over five hundred original drawings by Mr. William P. Didusch make this volume one of the best illustrated medical works we have seen.

Fifty-three personal cases form a unique collection of genital abnormalities and dysfunctions of the most unusual kinds. These rare anomalies are described as hermaphroditism, male and female pseudohermaphroditism, hermaphroditism verus, and adrenogenital syndrome, and the more common genital abnormalities such as hypospadias, epispadias, cryptorchidism, and so forth. The embryology of hermaphroditism is well described with clear diagrams and illustrations. This astonishing array of cases is illustrated by photographs and drawings, many of which were made at the operating table. Each step in the operating technic is portrayed clearly enough to aid anyone who attempts such surgery.

The anguish of the unfortunate individuals described by Dr. Young can be imagined. Boys have been brought up as girls only to discover that they had been wrongly classed sexually, or were of indeterminate sex. One patient was brought up in a male orphanage until operation disclosed a uterus, tube and ovary. The child was then dressed as a girl and transferred to a female orphanage. At the age of seventeen a hernia operation revealed that the supposed ovary was a testicle, and the patient again assumed male attire. Such are the tragedies Dr. Young has described. As a master craftsman he has righted the wrongs of nature by the many ingenious and original operative procedures, which he has so ably described in this book.

Minor Maladies and Their Treatment. Leonard Williams. Seventh edition. 439 pp. Baltimore: William Wood & Co., 1937. $3.75.

The author of this work gives as its raison d'etre the fact that when he went into practice he found himself moderately well equipped in the diagnosis and treatment of the diseases which he most seldom encountered, but ignorant in those matters about which he was frequently consulted. So this book is devoted to a discussion of such subjects as colds, coughs, sore throats, indigestion, constipation, neuralgia and headache. The author writes in a simple, conversational style and adds bits of experiences acquired through years of practice; still, it is rather surprising that a work like this has gone on to the seventh edition.

A Primer for Diabetic Patients: An outline of treatment for diabetes with diet, insulin and protamine zinc insulin including directions and charts for the use of physicians in planning diet prescriptions. Russell M. Wilder. Sixth edition reset. 191 pp. Philadelphia and London: W. B. Saunders Company, 1937. $1.75.

This new edition of Dr. Wilder's book was made necessary by the addition of protamine insulin in diabetic treatment. In the nine sections are given, in the simplest and most direct language, discussions of the nature of diabetes and its treatment by diet and insulin. Various important complications of diabetes, including a brief section on the hygiene of the feet, are given adequate space as well as special dietary problems for children and for weight reduction.

A Monograph on Veins. Kenneth J. Franklin. 410 pp. Springfield and Baltimore: Charles C Thomas, 1937. $6.00.

Dr. Franklin has long been a leader in investigation of the anatomy and physiology of the veins. His book is the culmination of many years of intensive work and brings together not only his own extensive experiences but also a complete review of the entire subject, a summary that is not to be found between the covers of any other volume. Known also for his interest in the history of medicine, there is a distinct historical trend to be noted on almost every page. Although perhaps primarily a book for the physiologist who is working on the functions of the veins, there is much material here that will interest the clinician who is actively interested in keeping in the front rank of research. The surgeon and the neurologist, moreover, will find much of value. The book, published in a sumptuous fashion, with excellent illustrations and replete with historical data, becomes a valuable part of the medical historian's library. Unique in character, reflecting sound research, this volume should have a wide appeal to the medical profession.

A Text-Book of Ophthalmic Operations. Harold Grimsdale and Elmore Brewerton. Third edition. 322 pp. Baltimore: William Wood & Co., 1937. $6.00.

This well-written third edition, containing 105 line drawings, constitutes an excellent manual for current practice in ophthalmic surgery. The first seven chapters deal with surgery of the ocular adnexa (muscles, eyelids, conjunctiva, lacrimal apparatus), including enucleation, and the remaining five chapters, comprising about one half the text, deal with surgery upon the eye itself (cataract, glaucoma, detached retina and intraocular foreign bodies).

If one comment were allowed for improvement in the text, it would seem to take the direction of a condensation of items of purely historical interest, and an elaboration of items in the last five chapters dealing with preoperative and postoperative care. For example, the utilization of biomicroscopy preoperatively and postoperatively and the interpretation of surgical complications in terms of tissue pathology would seem to add greatly to the usefulness of the text.

The Postmortem Examination. Sidney Farber. 201 pp. Springfield, Illinois, and Baltimore: Charles C Thomas, 1937. $3.50.

This is a scholarly piece of work which can be highly recommended. The book begins with a historical introduction, deals with the signs of death, the equipment for autopsy technic and care of bodies, the regulations governing postmortem examinations, the procedure of viewing a body, the removal of organs, their section, the examination of the skeleton, special technics including a short summary of medicolegal procedures, a chapter on postmortem examination in infants and children with appendices giving the weights of organs, the standard procedure for postmortem examinations as adopted by pathologists and undertakers in New York City and, finally, a copy of a typical autopsy protocol by Virchow.

There are minor faults, such as the implication that in adults the rib cartilages can be readily sectioned by a knife and the indication that removal of the organs of the neck is a standard and usual procedure in autopsy technic. However, these are of slight importance in a book which is remarkable for its thoroughness, its documentation with good bibliographies, and the practical character of its instruction.

The Traffic in Health. Charles Solomon. 393 pp. New York: Navarre Publishing Company, Inc., 1937. $2.75.

This book is put out with a gaudy jacket showing the silhouette of a cloaked skeleton holding a bottle which is surrounded by an effulgence which might be mistaken for a halo. It is extremely timely and is a mine of information. Unfortunately, the writing is dull and in catalogue fashion, classified according to the ailments which drugs are supposed to benefit. Many interesting facts are obtained by a study of this volume, all of them pointing to the great necessity of a revision of our laws to protect the public. Even though the reviewer has been in touch with this field for years, he found many new facts recorded in this book. It is worth the perusal of every physician in order that he may aid in the appropriate education of his patients and guard them from the unscrupulous manufacturers of patent medicines.

Materia Medica, Pharmacology, Therapeutics and Prescription Writing: For students and practitioners. Walter Arthur Bastedo. Fourth edition, reset. 778 pp. Philadelphia and London: W. B. Saunders Company, 1937. $6.50.

This is a new edition of a standard text brought well up-to-date, including even the recent work on sulfanilamide. The present edition follows the previous ones, and like all pharmacological texts, studies the complete action of each drug, grouping the various drugs according to their customary use or chief action in treatment. The therapeutic discussion is more extensive than in most English texts and is on the whole satisfactory though some of the recommendations would be disapproved in ultrascientific clinics. The discussion of flavoring and prescription writing is unusually clear.

The Endocrines in Theory and Practice. Articles republished from the *British Medical Journal.* 278 pp. Philadelphia: P. Blakiston's Son & Co., Inc., 1937. $3.50.

This book is a joint effort by the English workers in endocrinology to fill the crying need for something which the general practitioner can turn to in order to keep up-to-date in this field. It corresponds in many respects to *Glandular Physiology and Therapy,* published in 1935 by the American Medical Association, which comprised a series of similar articles by the American profession. The book is lucid, up-to-date, accurate, and not too comprehensive. Its list of authors includes the names of many who have contributed widely to endocrinology. It should be a valuable asset to anybody interested in this field.

The Baby's First Two Years. Richard M. Smith. 121 pp. Boston: Houghton-Mifflin Company, 1937. $1.75.

For more than two decades Dr. Smith's manual on infant care has been widely and favorably known in these parts. In many households it has been, so to speak, standard. And indeed it answers most of the questions concerning feeding, habits and general management which are likely to arise in the normal course of events. Its aim is to supplement, not to supplant, personal advice from the physician. For this latest edition the subject matter has been revised or entirely rewritten to accord with the most recent accepted opinion. Safe, sane and authoritative, this little book of reference can be enthusiastically recommended to anyone who is charged with the care of a baby.